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(54) **Title:** 4-BIARYLYL-1-PHENYLAZETIDIN-2-ONES

(57) **Abstract:** 4-Biarylyl-1-phenylazetidin-2-ones useful for the treatment of hypercholesterolemia are disclosed.

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4-BIARYLYL-1-PHENYLAZETIDIN-2-ONES

Field of the Invention

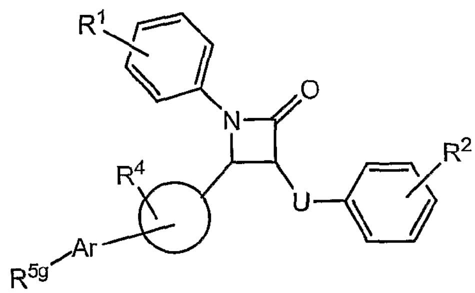
[0001] The invention relates to a chemical genus of 4-biarylyl-1-phenylazetidin-2-ones useful for the treatment of hypercholesterolemia and other disorders.

Background of the Invention

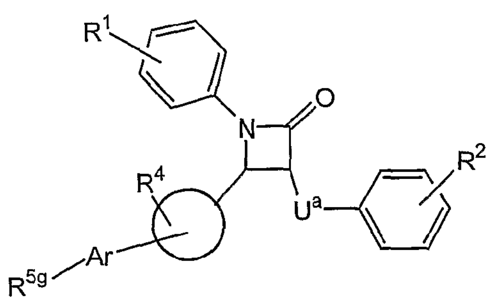
[0002] 1,4-Diphenylazetidin-2-ones and their utility for treating disorders of lipid metabolism are described in US patent 6,498,156, USRE37721 and PCT application WO02/50027, the disclosures of which are incorporated herein by reference as they relate to utility.

Summary of the Invention

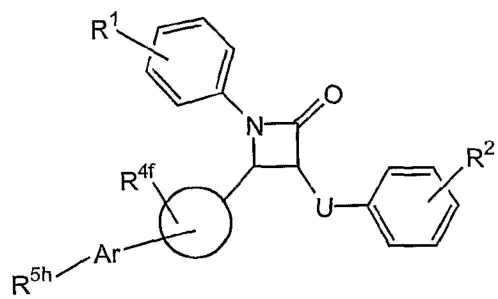
[0003] In one aspect the invention relates to compounds of formula:



which comprises compounds of two closely related genera, Φ and Ψ:

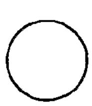


and



Φ Ψ

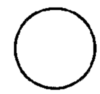
wherein

 represents an aryl or heteroaryl residue; Ar represents an aryl residue; R^1

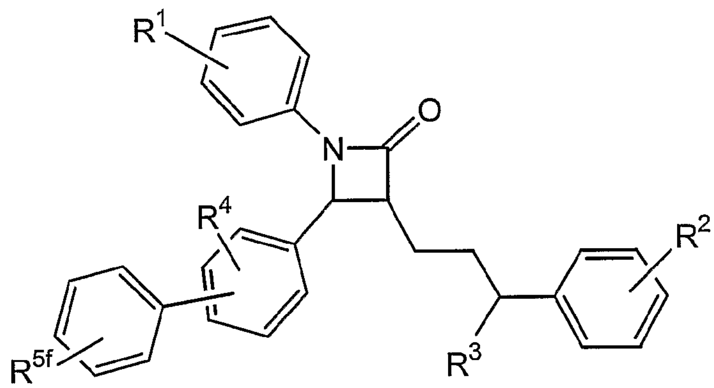
represents one, two, three, four or five residues chosen independently from H, halogen, -OH, loweralkyl, OCH_3, OCF_2H, OCF_3, CH_3, CF_2H, CH_2F, -O-loweralkyl, methylenedioxy, ethylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -SH, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, alkoxycarbonyl, carboxyalkyl, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy, $-PO_3H_2$, $-SO_3H$, $-B(OH)_2$, a sugar, a polyol, a glucuronide and a sugar carbamate; R^2 represents one, two, three, four or five residues chosen independently from H, halogen, -OH, loweralkyl, OCH_3, OCF_2H, OCF_3, CH_3, CF_2H, CH_2F, -O-loweralkyl, methylenedioxy, ethylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -SH, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, alkoxycarbonyl, carboxyalkyl, carboxamido, alkylsulfoxide, acylamino, amidino, $-PO_3H_2$, $-SO_3H$, $-B(OH)_2$, a sugar, a polyol, a glucuronide and a sugar carbamate; R^4 represents one, two, three or four residues chosen independently from H, halogen, -OH, loweralkyl, -O-loweralkyl, hydroxyloweralkyl, -CN, CF_3, nitro, -SH, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, alkoxycarbonyl, carboxyalkyl, carboxamido, alkylsulfoxide, acylamino, amidino, $-PO_3H_2$, $-SO_3H$, $-B(OH)_2$, a sugar, a polyol, a glucuronide and a sugar carbamate; R^{4f} is -OH, -SH or $-B(OH)_2$; R^{5g} represents one, two, three, four or five residues on Ar chosen independently from halogen, -OH, loweralkyl, -O-loweralkyl, methylenedioxy, ethylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -SH, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, alkoxycarbonyl, carboxyalkyl, carboxamido, alkylsulfoxide, acylamino, amidino, $-PO_3H_2$, $-SO_3H$, $-B(OH)_2$, a sugar, a polyol, a glucuronide and a sugar carbamate; R^{5h} represents one, two, three, four or five residues on Ar chosen independently from hydrogen, halogen, -OH, loweralkyl, -O-loweralkyl, methylenedioxy, ethylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -SH, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, alkoxycarbonyl,

carboxyalkyl, carboxamido, alkylsulfoxide, acylamino, amidino, $-PO_3H_2$, $-SO_3H$, $-B(OH)_2$, a sugar, a polyol, a glucuronide and a sugar carbamate; U is (C_2-C_6)-alkylene in which one or more $-CH_2-$ may be replaced by a radical chosen from -S-, -S(O)-, $-SO_2-$, -O-, -C(=O)-, -CHOH-, -NH-, CHF, CF_2, -CH(O-loweralkyl)-, -CH(O-loweracyl)-, $-CH(OSO_3H)-$, $-CH(OPO_3H_2)-$, $-CH(OB(OH)_2)-$, or -NOH-, with the provisos that (1) adjacent $-CH_2-$ residues are not replaced by -S-, -S(O)-, $-SO_2-$ or -O-; and (2) -S-, -S(O)-, $-SO_2-$, -O- and -NH- residues are not separated only by a single carbon; U^a is the same as U except that U^a excludes $-CH_2CH_2CH(OH)-$.

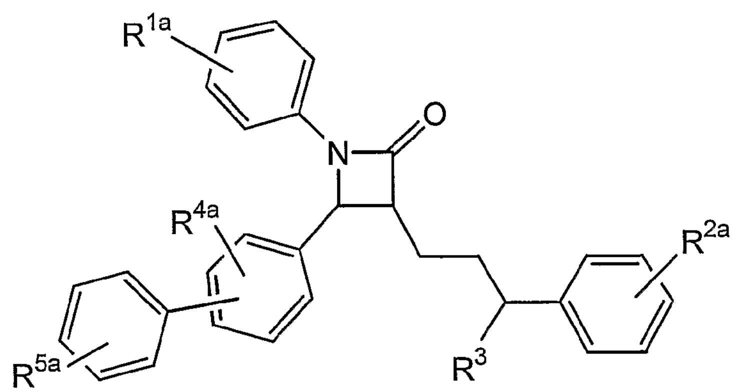
The genera Φ and Ψ exclude compounds in which R^{5g} is -CN; 2,5-dimethoxy; 2,6-dimethoxy or halogen when neither ring of the biphenyl residue is further substituted.

The genera Φ and Ψ also exclude compounds in which R^{5g} is 2-hydroxy when  represents a 2,5-thienyl residue.

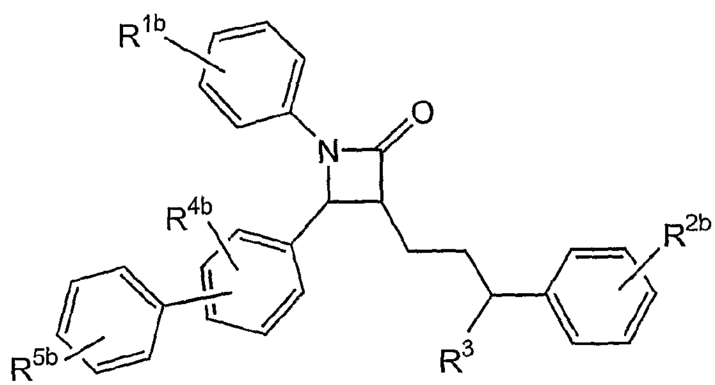
[0004] Subgenera include biphenyl compounds of general formulae I -VII:



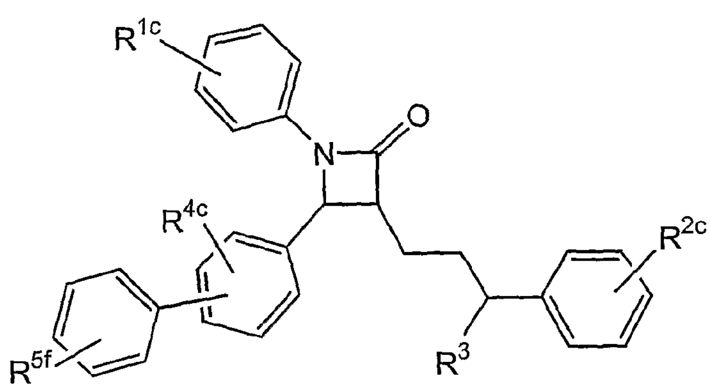
I



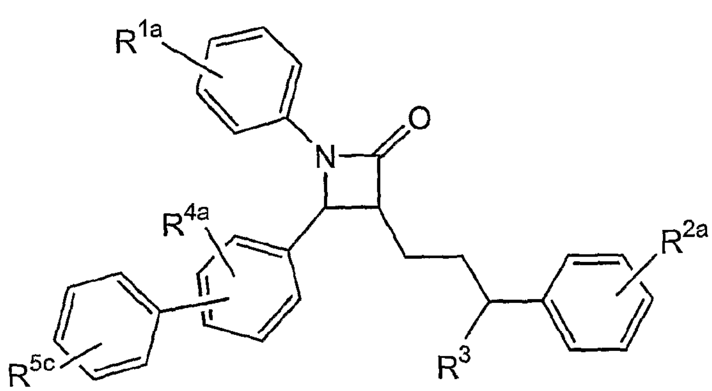
II



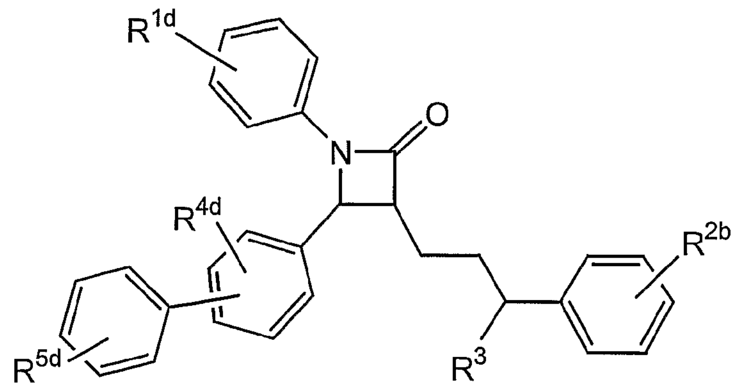
III



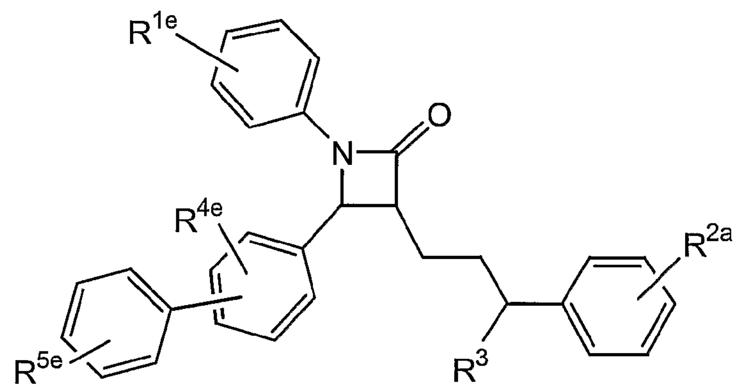
IV



V



VI



VII

[0005] In formula I, R^1 and R^2 represent one or two residues chosen independently from H, halogen, -OH, loweralkyl, OCH_3, OCF_2H, OCF_3, CH_3, CF_2H, CH_2F, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy, a sugar, a glucuronide and a sugar carbamate; R^3 is chosen from H, -OH, fluoro, -O-loweralkyl and -O-acyl; R^4 represents one, two, three or four residues chosen independently from H, halogen, -OH, loweralkyl, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy, a sugar, a glucuronide and a

sugar carbamate; R^{5f} represents one, two, three, four or five residues chosen independently from halogen, -OH, loweralkyl, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy, a sugar, a glucuronide a sugar carbamate and $-N^+R^6R^7R^8$ X^-; R^6 is C_1 to C_{20} hydrocarbon or forms a five- to seven-membered ring with R^7; R^7 is alkyl or forms a five- to seven-membered ring with R^6; R^8 is alkyl or together with R^6 or R^7 forms a second five- to seven-membered ring; and X is an anion.

[0006] In formula II one of R^{1a}, R^{4a} and R^{5a} is $-Q-A-N^+R^9R^{10}R^{11}$ X^- and the other two of R^{1a}, R^{4a} and R^{5a} are chosen independently from hydrogen, halogen, -OH, loweralkyl, OCH_3, OCF_2H, OCF_3, CH_3, CF_2H, CH_2F, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy. R^{2a} represents one or two residues chosen independently from H, halogen, -OH, loweralkyl, OCH_3, OCF_2H, OCF_3, CH_3, CF_2H, CH_2F, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy and benzyloxy. R^3 is chosen from H, -OH, fluoro, -O-loweralkyl and -O-acyl. Q is chosen from a direct bond, -O-, -S-, -NH-, $-CH_2O-$, $-CH_2NH-$, -C(=O)-, -CONH-, -NHCO-, -O(C=O)-, -(C=O)O-, -NHCONH-, -OCONH- and -NHCOO-. A is chosen from C_2 to C_{20} hydrocarbon, substituted alkyl of 2 to 20 carbons, substituted aryl, substituted arylalkyl, and oxaalkyl of four to fifty carbons; and, when Q is a direct bond, -C(=O) or –O(C=O)-, A may additionally be methylene. R^9 is C_1 to C_{20} hydrocarbon or forms a five- to seven-membered ring with A or R^{10}; R^{10} is alkyl, forms a double bond with A or forms a five- to seven-membered ring with R^9; R^{11} is alkyl or together with R^{10} or R^9 forms a second five- to seven-membered ring; and X is an anion.

[0007] In formula III, R^{2b} represents one or two residues chosen independently from H, halogen, -OH, loweralkyl, OCH_3, OCF_2H, OCF_3, CH_3, CF_2H, CH_2F, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy. R^3 is chosen from H, -OH, fluoro, -O-loweralkyl and -O-acyl. One of R^{1b}, R^{4b} and R^{5b} is R^{12} and the other two of R^{1b}, R^{4b} and R^{5b} are chosen independently from hydrogen, halogen, -OH, loweralkyl, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy, a sugar, a glucuronide, and a sugar carbamate; R^{12} is (C_0 to C_{30})alkylene-G_n in which one or more $-CH_2-$ residues in said alkylene may be replaced by -S-, -SO-, SO_2-, -O-, -NH-, -N(alkyl)-, -N(phenyl)-, -N(alkylphenyl)-, $-N^+(alkyl)_2-$, $-N^+(phenyl)_2-$, $-N^+(alkylphenyl)_2-$, -C(=O)-, -C(=S), CH=CH-, -C=C-, phenylene or -N[(C=O)alkyleneCOOH]-; G is chosen from $-SO_3H$, $-PO_3H_2$, $-O-PO_3H_2$, -COOH, $-C(N=H)NH_2$, a polyol, a sugar, a glucuronide, a sugar carbamate, $-N^+R^{6a}R^{7a}R^{8a}\ X^-$, and a mono or bicyclic trialkylammoniumalkyl residue; R^{6a} is C_1 to C_{20} hydrocarbon; R^{7a} is alkyl; R^{8a} is alkyl; n is one, two, three, four or five and X is an anion.

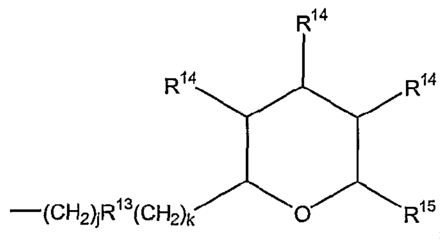
[0008] In compounds of formula IV, R^{1c} and R^{2c} represent one or two residues chosen independently from H, halogen, -OH, loweralkyl, OCH_3, OCF_2H, OCF_3, CH_3, CF_2H, CH_2F, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, hydroxyamidino, guanidino, dialkylguanidino, phenyl, benzyl, phenoxy, benzyloxy, a glucuronide, and a sugar carbamate. R^3 is chosen from H, -OH, fluoro, -O-loweralkyl and -O-acyl. R^{4c} represents one, two, three or four residues chosen independently from H, halogen, -OH, loweralkyl, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -

S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy, a glucuronide and a sugar carbamate; and R^{5f} represents one, two, three, four or five residues chosen independently from halogen, -OH, loweralkyl, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy, a sugar, a glucuronide a sugar carbamate and - $N^+R^6R^7R^8\ X^-$.

[0009] In compounds of formula V, R^{1a}, R^{2a} and R^{4a} each represents one or two residues chosen independently from H, halogen, -OH, loweralkyl, OCH_3, OCF_2H, OCF_3, CH_3, CF_2H, CH_2F, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy. R^3 is chosen from H, -OH, fluoro, -O-loweralkyl and -O-acyl. R^{5c} is $-Q-A-N^+R^9R^{10}R^{11}\ X^-$; Q is chosen from a direct bond, -O-, -S-, -NH-, $-CH_2O-$, $-CH_2NH-$, -C(=O)-, -CONH-, -NHCO-, $-CH_2NH(C=O)-$, -O(C=O)-, -(C=O)O-, -NHCONH-, -OCONH- and -NHCOO- ; and A is chosen from C_2 to C_{20} hydrocarbon, substituted alkyl of 2 to 20 carbons, substituted aryl, substituted arylalkyl, and oxaalkyl of four to fifty carbons; and, when Q is a direct bond, -C(=O) or –O(C=O)-, A may additionally be methylene.

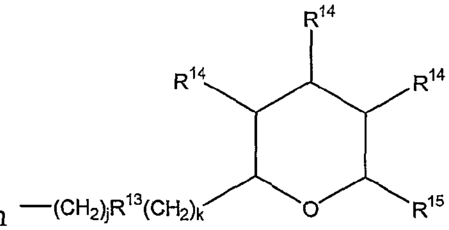
[0010] In compounds of formula VI, R^{2b} represents one or two residues chosen independently from H, halogen, -OH, loweralkyl, OCH_3, OCF_2H, OCF_3, CH_3, CF_2H, CH_2F, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy. R^3 is chosen from H, -OH, fluoro, -O-loweralkyl and -O-acyl. One of R^{1d}, R^{4d} and R^{5d} is R^{12a} and the other two of R^{1d}, R^{4d} and R^{5d} are chosen independently

from hydrogen, halogen, -OH, loweralkyl, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy and R^{12a};

R^{12a} is 

, or, when R^{5d} is R^{12a}, R^{12a} may additionally be (C_0 to C_{30})alkylene-G_n in which one or more $-CH_2-$ residues in said alkylene may be replaced by -S-, -SO-, SO_2-, -O-, -NH-, -N(alkyl)-, -N(phenyl)-, -N(alkylphenyl)-, $-N^+(alkyl)_2-$, $-N^+(phenyl)_2-$, $-N^+(alkylphenyl)_2-$, -C(=O)-, -C(=S), CH=CH-, -C≡C-, phenylene or -N[(C=O)alkyleneCOOH]-; G is chosen from $-SO_3H$, $-PO_3H_2$, $-O-PO_3H_2$, -COOH, $-C(N=H)NH_2$, a polyol, a sugar, a glucuronide, a sugar carbamate, $-N^+R^{6a}R^{7a}R^{8a}\ X^-$, and a mono or bicyclic trialkylammoniumalkyl residue; R^{13} is chosen from a direct bond, -C≡C-, $-OCH_2$, -C(=O)- and -CHOH-; R^{14} is chosen from -OH and -OC(=O)alkyl; R^{15} is chosen from $-CH_2OH$, $-CH_2OC(=O)$alkyl and -COOalkyl; j is 1-5; k is zero or 1-5; and n is 1-5.

[0011] In compounds of formula VII, R^{1e}, R^{2a} and R^{4e} each represents one or two residues chosen independently from H, halogen, -OH, loweralkyl, OCH_3, OCF_2H, OCF_3, CH_3, CF_2H, CH_2F, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy. R^3 is chosen from H, -OH, fluoro, -O-loweralkyl and -O-acyl.

R^{5e} is chosen from 

and (C_0 to C_{30})alkylene-G_n in

which one or more $-CH_2-$ residues in said alkylene may be replaced by -S-, -SO-, SO_2-, -O-, -NH-, -N(alkyl)-, -N(phenyl)-, -N(alkylphenyl)-, $-N^+(alkyl)_2-$, $-N^+(phenyl)_2-$, -$N^+(alkylphenyl)_2-$, -C(=O)-, -C(=S), CH=CH-, -C=C-, phenylene or -N[(C=O)alkyleneCOOH]-.

[0012] The invention also includes pharmaceutically acceptable salts thereof, in any stereoisomeric form, or a mixture of any such compounds in any ratio.

[0013] The compounds described herein can be included in pharmaceutical formulations comprising a pharmaceutically acceptable carrier and one or more of: (1) a dyslipidemic agent, (2) an anti-diabetic agent, (3) an anti-hypertensive agent, (4) an anti-obesity agent, (5) an agent used to treat autoimmune disorders, (6) an agent used to treat demylenation and its associated disorders, (7) an agent used to treat Alzheimer's disease, (8) a blood modifier, (9) a hormone replacement agent/composition, (10) a chemotherapeutic agent, (11) a peptide which mitigates one or more symptoms of atherosclerosis, (12) an anti-cancer agent, (13) an agent used to treat bone loss and associated disorders, and (14) other agents.

[0014] The compounds and pharmaceutical formulations described herein can be used in methods for treating a condition for which a cholesterol absorption inhibitor is indicated; preventing or treating a cholesterol related disease; inhibiting the absorption of or reducing plasma or tissue concentration of one or more sterols or stanols; preventing or treating sistoserolemia; preventing or treating vascular diseases/disorders and conditions, dyslipidemia, mixed dyslipidemia, hypo α-lipoproteinemia, LDL pattern B, LDL pattern A, primary dysbetalipoproteinemia (Frederickson Type III), hyperlipidemia (including but not limited to hypercholesterolemia, hypertriglyceridemia, sitosterolemia), hypertension, angina pectoris, cardiac arrhythmias, congestive heart failure, and stroke; reducing the incidence of cardiovascular disease-related events; preventing or treating vascular conditions and associated thrombotic events; preventing or treating vascular inflammation; reducing blood plasma or serum concentrations of C-reactive protein; preventing, treating, or ameliorating symptoms of Alzheimer's Disease (AD); regulating production or levels of at least one amyloid β (Aβ) peptide; regulating the amount of ApoE isoform 4 in the bloodstream and/or brain; preventing or treating

cognitive related disorders (including dementia); preventing or treating obesity; preventing or decreasing the incidence of xanthomas; preventing or minimizing muscular degeneration and related side effects associated with certain HMG-CoA reductase inhibitors (statins); preventing or treating diabetes and associated conditions; preventing or treating at least one autoimmune disorder; preventing or treating demyelination and associated disorders; preventing or treating cholesterol associated tumors; inhibiting the expression of at least one multiple ("multi")-drug resistance gene or protein in an animal cell; enhancing the effectiveness of a chemotherapeutic agent in a subject having cancer; reversing a multi-drug resistance phenotype exhibited by an animal cell; modulating lipid raft structure; and preventing or treating osteopenia disorders (bone loss disorders). The methods comprise administering a therapeutically effective amount of a compound or pharmaceutical formulation described herein.

[0015] The invention relates to an article of manufacture comprising a container, instructions, and a pharmaceutical formulation as described above. The instructions are for the administration of the pharmaceutical formulation for a purpose chosen from: treating a condition for which a cholesterol absorption inhibitor is indicated; preventing or treating a cholesterol related disease; inhibiting the absorption of or reducing plasma or tissue concentration of one or more sterols or stanols; preventing or treating sistoserolemia; preventing or treating vascular diseases/disorders and conditions, dyslipidemia, mixed dyslipidemia, hypo α-lipoproteinemia, LDL pattern B, LDL pattern A, primary dysbetalipoproteinemia (Frederickson Type III), hyperlipidemia (including but not limited to hypercholesterolemia, hypertriglyceridemia, sitosterolemia), hypertension, angina pectoris, cardiac arrhythmias, congestive heart failure, and stroke; reducing the incidence of cardiovascular disease-related events; preventing or treating vascular conditions and associated thrombotic events; preventing or treating vascular inflammation; reducing blood plasma or serum concentrations of C-reactive protein; preventing, treating, or ameliorating symptoms of Alzheimer's Disease (AD); regulating production or levels of at least one amyloid β (Aβ) peptide; regulating the amount of ApoE isoform 4 in the bloodstream and/or brain; preventing or treating cognitive related disorders

(including dementia); preventing or treating obesity; preventing or decreasing the incidence of xanthomas; preventing or minimizing muscular degeneration and related side effects associated with certain HMG-CoA reductase inhibitors (statins); preventing or treating diabetes and associated conditions; preventing or treating at least one autoimmune disorder; preventing or treating demyelination and associated disorders; preventing or treating cholesterol associated tumors; inhibiting the expression of at least one multiple ("multi")-drug resistance gene or protein in an animal cell; enhancing the effectiveness of a chemotherapeutic agent in a subject having cancer; reversing a multi-drug resistance phenotype exhibited by an animal cell; modulating lipid raft structure; treating or preventing a diseasee associated with lipid raft structure; and preventing or treating osteopenia disorders (bone loss disorders).

[0016] These and other embodiments of the present invention will become apparent in conjunction with the description and claims that follow.

Brief Description Of Drawings

[0017] FIG. 1 is a table providing bioavailability data for several compounds of the invention.

[0018] FIG. 2 is a table providing ACAT inhibition data for several compounds of the invention.

[0019] FIG. 3A and 3B are graphs depicting ^{3}H-(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol binding to the small intestine of hamsters in the presence or absence of competitor compounds.

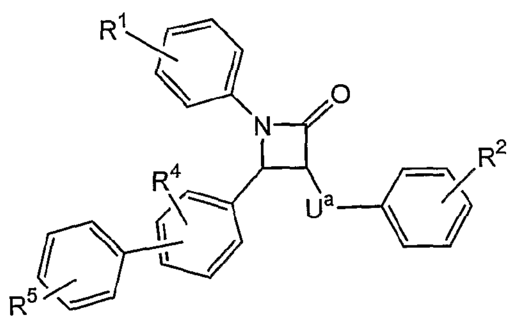
[0020] FIG. 3C is a table showing the calculated percentage binding relative to control, based on the results depicted in FIG. 3A and FIG. 3B.

[0021] FIG. 4A-D are tables showing the results of retinal, taurocholic acid, progeseterone, sitostanol and cholesterol absorption assays.

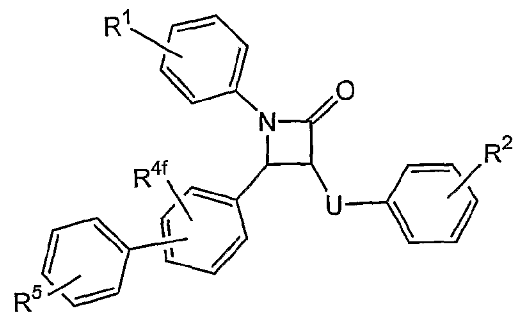
[0022] FIG. 5A-C are plots of the additivity assays using the rat cholesterol absorption model.

Detailed description of the Invention

[0023] Compounds of the genus represented by formulae Φ, Ψ, and I - VIII above are inhibitors of cholesterol absorption from the intestine. As such they have utility in treating and preventing lipid disorders, such as hypercholesterolemia and hyperlipidemia. Because of their effect in lowering serum lipids, the compounds are useful in the treatment and prevention of atherosclerosis. Subgenera according to the invention include compounds of formulae Φ and Ψ in which U is chosen from-$CH_2CH_2CH(OH)$-, -SCH_2CH_2-, -$S(O)CH_2CH_2$-, -$SCH_2C(=O)$-, -$SCH_2CH(OH)$-, -$CH(OH)CH_2CH_2$- and -$(CH_2)_4$-, wherein the left end of the string is the point of attachment to the azetidinone ring and the right end of the string is the point of attachment to the phenyl ring. Other subgenera of compounds of formulae Φ and Ψ include ΦA and ΨA

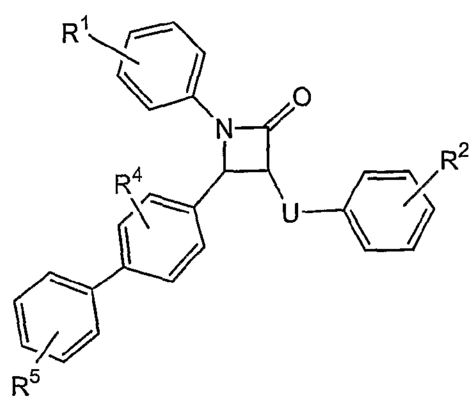


and



ΦA ΨA

[0024] Futher subgenera include compounds of formulae ΦA and ΨA in which the ring bearing R^5 is in the para position, e.g.:

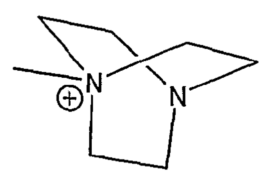


.

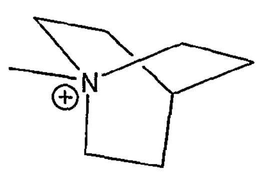
In another subgenus R^1 may be H or 4-fluoro; R^2 may be 4-fluoro; and R^4 may be H or

hydroxy. In another subgenus, R^4 and R^5 are both hydroxy.

[0025] Other subgenera according to the invention include compounds in which R^1, R^{1a}, R^2, R^{2a}, R^4 and R^{4a} are chosen independently from H, halogen, -OH, and methoxy; compounds in which R^1, R^2, R^4 and R^5 are chosen from H, a sugar, a glucuronide and a sugar carbamate; compounds in which R^3 is chosen from hydrogen and hydroxy; compounds in which R^4 or R^{4a} is hydrogen; compounds in which R^5 or R^{5a} is chosen from halogen, hydroxy, loweralkyl, -O-loweralkyl, CF_3, alkylsulfonyl and arylsulfonyl. Examples of compounds of formula II include those in which one of R^{1a}, R^{4a} and R^{5a} is $-Q-A-N^+R^9R^{10}R^{11}\ X^-$ and -Q-A- is chosen from (C_2 to C_{20} hydrocarbon), -O-(C_2 to C_{20} hydrocarbon), -NH(C_2 to C_{20} hydrocarbon), -NHCO(C_2 to C_{20} hydrocarbon) and oxaalkyl of four to twenty carbons. In this series of compounds, R^9,R^{10} and R^{11} are (1) loweralkyl or benzyl, or (2) R^9,R^{10} and R^{11} taken together form a diazabicyclooctane quat:



or (3) R^9,R^{10} and R^{11} taken together form a quinuclidinium quat:



[0026] Some of the compounds of the invention are quaternary salts, i.e. cationic species. Therefore they will always be presented as salts. Other compounds of formula I may contain basic or acidic residues, allowing them to be presented as salts. In the claims, reference to the acid includes its salts. Thus, for example, a claim to 4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-sulfonic acid is intended to encompass as well sodium 4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-sulfonate. The term "pharmaceutically acceptable salt" refers to salts whose counter ion derives from pharmaceutically acceptable non-toxic acids and bases. When the compounds contain a quat or a basic residue, suitable

pharmaceutically acceptable base addition salts for the compounds of the present invention include inorganic acids, organic acids and, in the case of quats, water (which formally furnishes the hydroxide anion). Examples include hydroxide, acetate, benzenesulfonate (besylate), benzoate, bicarbonate, bisulfate, carbonate, camphorsulfonate, citrate, ethanesulfonate, fumarate, gluconate, glutamate, glycolate, bromide, chloride, isethionate, lactate, maleate, malate, mandelate, methanesulfonate, mucate, nitrate, pamoate, pantothenate, phosphate, succinate, sulfate, tartrate, trifluoroacetate, p-toluenesulfonate, acetamidobenzoate, adipate, alginate, aminosalicylate, anhydromethylenecitrate, ascorbate, aspartate, calcium edetate, camphorate, camsylate, caprate, caproate, caprylate, cinnamate, cyclamate, dichloroacetate, edetate (EDTA), edisylate, embonate, estolate, esylate, fluoride, formate, gentisate, gluceptate, glucuronate, glycerophosphate, glycolate, glycollylarsanilate, hexylresorcinate, hippurate, hydroxynaphthoate, iodide, lactobionate, malonate, mesylate, napadisylate, napsylate, nicotinate, oleate, orotate, oxalate, oxoglutarate, palmitate, pectinate, pectinate polymer, phenylethylbarbiturate, picrate, pidolate, propionate, rhodanide, salicylate, sebacate, stearate, tannate, theoclate, tosylate, and the like. When the compounds contain an acidic residue, suitable pharmaceutically acceptable base addition salts for the compounds of the present invention include ammonium, metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Other base addition salts includes those made from: arecoline, arginine, barium, benethamine, benzathine, betaine, bismuth, clemizole, copper, deanol, diethylamine, diethylaminoethanol, epolamine, ethylenediamine, ferric, ferrous, glucamine, glucosamine, histidine, hydrabamine, imidazole, isopropylamine, manganic, manganous, methylglucamine, morpholine, morpholineethanol, n-ethylmorpholine, n-ethylpiperidine, piperazine, piperidine, polyamine resins, purines, theobromine, triethylamine, trimethylamine, tripropylamine, trolamine, and tromethamine.

[0027] In certain subgenera of compounds of formulae III, VI and VII, R^{1b} is R^{12} ;R^{2b} and R^{4b} are chosen from H, halogen, -OH, and methoxy; R^{12} is (C_6 to

C_{20})alkylene-G in which one or more $-CH_2-$ residues in said alkylene may be replaced by -O-, -NH-, -N(alkyl)-, -C(=O)- or -CH=CH-; and G is chosen from $-SO_3H$, a polyol, and a sugar. In a further embodiment, R^5 is R^{12} ; R^1, R^2 and R^4 are chosen from H, halogen, -OH, and methoxy; R^{12} is (C_6 to C_{20})alkylene-G in which one or more $-CH_2-$ residues in said alkylene may be replaced by -O-, -NH-, -N(alkyl)-, -C(=O)- or -CH=CH-; and G is chosen from $-SO_3H$, a polyol, and a sugar.

Therapeutic Indications

[0028] The present invention further provides methods for treating a condition for which a cholesterol absorption inhibitor is indicated; preventing or treating a cholesterol related disease; inhibiting the absorption of or reducing plasma or tissue concentration of one or more sterols or stanols; preventing or treating sistoserolemia; preventing or treating vascular diseases/disorders and conditions, dyslipidemia, mixed dyslipidemia, hypo α-lipoproteinemia, LDL pattern B, LDL pattern A, primary dysbetalipoproteinemia (Frederickson Type III), hyperlipidemia (including but not limited to hypercholesterolemia, hypertriglyceridemia, sitosterolemia), hypertension, angina pectoris, cardiac arrhythmias, congestive heart failure, and stroke; reducing the incidence of cardiovascular disease-related events; preventing or treating vascular conditions and associated thrombotic events; preventing or treating vascular inflammation; reducing blood plasma or serum concentrations of C-reactive protein; preventing, treating, or ameliorating symptoms of Alzheimer's Disease (AD); regulating production or levels of at least one amyloid β (Aβ) peptide; regulating the amount of ApoE isoform 4 in the bloodstream and/or brain; preventing or treating cognitive related disorders (including dementia); preventing or treating obesity; preventing or decreasing the incidence of xanthomas; preventing or minimizing muscular degeneration and related side effects associated with certain HMG-CoA reductase inhibitors (statins); preventing or treating diabetes and associated conditions; preventing or treating at least one autoimmune disorder; preventing or treating demyelination and associated disorders; preventing or treating cholesterol associated tumors; inhibiting the expression of at least one multiple ("multi")-drug resistance gene or protein in an animal cell; enhancing the effectiveness of a

chemotherapeutic agent in a subject having cancer; reversing a multi-drug resistance phenotype exhibited by an animal cell; modulating lipid raft structure; and preventing or treating osteopenia disorders (bone loss disorders). The methods comprise administering a therapeutically effective amount of a compound described herein.

[0029] The compounds described herein may inhibit cholesterol absorption and thus reduce cholesterol levels in vivo. The compositions and therapeutic methods described herein are useful for treating any condition for which a cholesterol absorption inhibitor is indicated. When administered to a patient, the compositions and pharmaceutical formulations described herein can lead to one or more of: reduced blood plasma or serum concentrations of low-density lipoprotein cholesterol (LDL-C); reduced blood plasma or serum concentrations of very low-density lipoprotein cholesterol (VLDL-C); reduced blood plasma or serum concentrations of intermediate-density lipoprotein cholesterol (IDL-C); reduced concentrations of cholesterol and cholesterol ester in the blood plasma or serum; reduced blood plasma or serum concentrations of apolipoprotein B; reduced blood plasma or serum concentrations of triglycerides; increased clearance of triglycerides; increased blood plasma or serum concentrations of high density lipoprotein cholesterol (HDL-C); reduced blood plasma or serum concentrations of non high-density lipoprotein cholesterol (non HDL-C); reduced levels of lipoprotein(a) (Lp(a)); increased ratio of HDL-C to LDL-C; inhibition of saponified and/or non-saponified fatty acid synthesis; reduced blood plasma or serum concentrations apolipoprotein C-II; reduced blood plasma or serum concentrations apolipoprotein C-III; increased blood plasma or serum concentrations of HDL associated proteins (including but not limited to apo A-I, apo A-II, apo A-IV, and apo E), and increased fecal excretion of cholesterol.

[0030] The compounds and pharmaceutical formulations described herein can be used alone or in combination therapy with one or more additional agents (e.g., one or more dyslipidemic agents, peptides which mitigates one or more symptoms of atherosclerosis, other agents, including combinations thereof) to prevent or treat a cholesterol related disease. Cholesterol related diseases include but are not limited to diseases involving elevated levels of LDL cholesterol, diseases involving regulation of LDL receptors, diseases involving reduced levels of HDL cholesterol, dyslipidemia,

diseases involving elevated levels of non-esterified fatty acids, diseases involving reduced or deficient lipoprotein lipase levels or activity (including reductions or deficiencies resulting from lipoprotein lipase mutations), diseases involving elevated levels of ketone bodies (e.g., β-OH butyric acid), hyperlipidemia, elevated LDL Pattern B, elevated LDL Pattern A, primary dysbetalipoproteinemia (Frederickson Type III), hypercholesterolemia, hypo α.-lipoproteinemia (low HDL cholesterol syndrome), hyperlipoproteinemia, elevated Lp(a) levels, hypertriglyceridemia (including Frederickson typse IV and V), other aberrations of apolipoprotein B metabolism, homozygous familial hypercholesterolemia, heterozygous familial hypercholesterolemia, presumed familial combined and non-familial (non-FH) forms of primary hypercholesterolemia (including Frederickson Types IIa and IIb), cholesterol ester storage disease, and cholesterol ester transfer protein disease.

[0031] The compounds and pharmaceutical formulations described herein can be used alone or in combination therapy with one or more additional agents (e.g., one or more dyslipidemic agents, peptides which mitigates one or more symptoms of atherosclerosis, other agents, including combinations thereof) to inhibit the absorption of or reduce plasma or tissue concentration of one or more sterols (referring to, for example: (from any source and in any form: α, β and γ) saturated or hydrogenated sterols including all natural or synthesized forms and derivatives thereof, and isomers including but not limited to cholesterol, sitosterol, campesterol, stigmasterol, brassicasterol (including dihydrobrassicasterol), desmosterol, chalinosterol, poriferasterol, clionasterol, ergosterol, coprosterol, codisterol, isofucosterol, fucosterol, clerosterol, nervisterol, lathosterol, stellasterol, spinasterol, chondrillasterol, peposterol, avenasterol, isoavenasterol, fecosterol, pollinastasterol) or stanols (referring to, for example: (from any source and in any form: α, β and γ) saturated or hydrogenated stanols including all natural or synthesized forms and derivatives thereof, and isomers, including but not limited to sitostanol, campestanol, stigmastanol, brassicastanol (including dihydrobrassicastanol), desmostanol, chalinostanol, poriferastanol, clionastanol, ergostanol, coprostanol, codistanol, isofucostanol, fucostanol, clerostanol, nervistanol, lathostanol, stellastanol, spinastanol, chondrillastanol, pepostanol, avenastanol, isoavenastanol, fecostanol, and

pollinastastanol and 5α-stanols (e.g., cholestanol, 5α-campestanol, 5α-sitostanol) or mixtures thereof in a subject in need of such treatment, for example, a sitosterolemic subject. Sterols and stanols also include free sterols and stanols, esterified sterols and stanols with aliphatic or aromatic acids (thereby forming aliphatic or aromatic esters, respectively), phenolic acid esters, cinnamate esters, ferulate esters, phytosterol and phytostanol glycosides and acylated glycosides or acylglycosides. Thus, terms the sterols and stanols encompasses all analogues, which may further have a double bond at the 5-position in the cyclic unit as in most natural sterols, or one or more double bonds at other positions in the rings (for example, 6,7, 8(9), 8(14), 14 5/7) or no double bonds in the cyclic unit as in stanols.

[0032] The compounds and pharmaceutical formulations described herein can be used alone or in combination therapy with one or more additional agents (e.g., one or more dyslipidemic agents, peptides which mitigates one or more symptoms of atherosclerosis, other agents, including combinations thereof) to prevent or treat sistoserolemia in patients who are either at risk of developing sistoserolemia or already exhibit sistoserolemia, for example, as described in US20020169134. Sitosterolemia is a genetic lipid storage disorder characterized by increased levels of sitosterol and other plant sterols in the plasma and other tissues due to increased non-selective intestinal absorption of sterols and decreased hepatic removal. Individuals having sitosterolemia can exhibit one or more of the following conditions: tendon and tuberous xanthomas, arthritis, hemolytic episodes, accelerated atherosclerosis and myocardial infarctions, and can die at an early age due to extensive coronary atherosclerosis (see Nguyen et al. 1991 Journal of Lipid Research, 32: 1941-1948).

[0033] The compounds and pharmaceutical formulations described herein can be used alone or in combination therapy with one or more additional agents (e.g., one or more anti-hypertensive agents, dyslipidemic agents, peptides which mitigates one or more symptoms of atherosclerosis, other agents, including combinations thereof) to prevent or treat vascular diseases/disorders and conditions (including but not limited to arteriosclerosis, atherosclerosis, acute vascular syndromes, peripheral arterial disease, cardiovascular disease, cerebrovascular disease (e.g., cerebral infarction or stroke (caused by vessel blockage or hemmorage), or transient ischemia attack (TIA),

syncope, atherosclerosis of the intracranial and/or extracranial arteries, and the like), renovascular disease, mesenteric vascular disease, pulmonary vascular disease, ocular vascular disease, microvascular disease (such as nephropathy, neuropathy, retinopathy), and peripheral vascular disease), hyperlipidemia (including but not limited to hypercholesterolemia, hypertriglyceridemia, sitosterolemia), hypertension, angina pectoris (including stable, chronic stable, vasospastic, and unstable angina), cardiac arrhythmias, congestive heart failure, and stroke in patients who are at risk for such a disease/condition or in need of such treatment for example, as described, in US2002147184 and US20030069221. Vascular disease is a term that broadly encompasses all disorders of blood vessels including small and large arteries and veins and blood flow. The most prevalent form of vascular disease is arteriosclerosis, a condition associated with the thickening and hardening of the arterial wall. Arteriosclerosis of the large vessels is referred to as atherosclerosis. Atherosclerosis is the predominant underlying factor in vascular disorders e.g., coronary artery disease, aortic aneurysm, arterial disease of the lower extremities and cerebrovascular disease. Other vascular conditions frequently coexist with cholesterol levels associated with atherosclerosis. These may include hypertension, angina and/or arrhythmia. Vascular conditions may be caused or aggravated by hypertension which is defined as persistently high blood pressure. Generally, adults are classified as being hypertensive when systolic blood pressure is persistently above 140 mmHg or when diastolic blood pressure is above 90 mmHG. Elevated blood pressure is a risk factor for atherosclerosis, cardiovascular and cerebrovascular disease.

[0034] The compounds and pharmaceutical formulations described herein can be used alone or in combination therapy with one or more additional agents (e.g., one or more anti-hypertensive agents, dyslipidemic agents, peptides which mitigates one or more symptoms of atherosclerosis, other agents, including combinations thereof) to reduce the incidence of cardiovascular disease-related events, for example, as described in US20050080071. Thus the compounds and pharmaceutical formulations described herein can be used to prevent or reduce the risk of an occurrence of a fatal or non-fatal cardiovascular event in patients having no history of clinically evident coronary heart disease, as well as patients having a history of clinically evident

coronary heart disease (CHD). A total cholesterol level in excess of 225-250 mg/dl is associated with significant elevation of risk of CHD. The newly revised NCEP ATP III low density lipoprotein (LDL-C) goal for patients with CHD or CHD risk equivalent is <100 mg/dL (2.59 mmol/L), for individuals with two or more risk factors is <130 mg/dL (3.37 mmol/L) and for individuals with fewer than two risk factors is <160 mg/dL (4.14 mmol/L). The phrase "cardiovascular event" includes but is not limited to fatal and non-fatal acute major coronary events, coronary revascularization procedures, myocardial revascularization procedures, peripheral vascular disease, stable angina and cerebrovascular insufficiency e.g., stroke. The phrase "acute major coronary event" includes fatal myocardial infarction, witnessed and unwitnessed cardiac death and sudden death occurring from 1 hour up to 24 hours after collapse, non-fatal myocardial infarction including definite acute Q-wave myocardial infarction, non-Q-wave myocardial infarction, and silent subclinical (remote) myocardial infarction, and unstable angina pectoris. Myocardial infarction includes recurrent myocardial infarction, Q-wave myocardial infarction, non-Q-wave myocardial infarction and silent subclinical (remote) myocardial infarction. The compounds and formulations described herein can be used alone or in combination therapy with one or more additional agents (e.g., one or more blood modifiers, anti-hypertensive agents, dyslipidemic agents, peptides which mitigates one or more symptoms of atherosclerosis, other agents, including combinations thereof) to reduce the risk of mortality following a myocardial infarction or other cardiovascular or acute major coronary event. In certain embodiments, the compound or formulation (e.g., compound of the invention with a statin (e.g., atorvastatin, rosuvastatin, simvastatin, lovastatin)) is administered within 6, 12, 18, 24, 36, or 48 hours after hospital admission for a myocardial infarction or other cardiovascular or acute major coronary event (Fonarow GC 2005 Chest 128:3641-51). In some embodiments the compound or formulation is administered within 24 hours after hospital admission. In some embodiments the compound or formulation is administered at any time before hospital discharge. In some embodiments the formulation consists, consists essentially of, or comprises ezetimibe. In some embodiments the formulation consists, consists essentially of, or comprises Vytorin (ezetimibe and simvastatin). In some

embodiments the formulation consists, consists essentially of, or comprises ezetimibe and one or more blood modifiers, anti-hypertensive agents, dyslipidemic agents (e.g., a statin such as atorvastatin, rosuvastatin), peptides which mitigates one or more symptoms of atherosclerosis, other agents, including combinations thereof.

[0035] The compounds and formulations described herein can used alone or in combination therapy with one or more additional agents (e.g., one or more blood modifiers, anti-hypertensive agents, dyslipidemic agents, peptides which mitigates one or more symptoms of atherosclerosis, other agents, including combinations thereof) to reverse or partially reverse the build-up of plaque in coronary arteries and thus may be associated with reduced plaque volume. In some embodiments, administration of the compounds or formulations described herein stops the progression of heart diease, leads to regression of heart disease. In some embodiments the formulation consists, consists essentially of, or comprises ezetimibe. In some embodiments the formulation consists, consists essentially of, or comprises Vytorin (ezetimibe and simvastatin). In some embodiments the formulation consists, consists essentially of, or comprises ezetimibe and one or more blood modifiers, anti-hypertensive agents, dyslipidemic agents (e.g., a statin such as atorvastatin, rosuvastatin), peptides which mitigates one or more symptoms of atherosclerosis, other agents, including combinations thereof.

[0036] The compounds and pharmaceutical formulations described herein can be used alone or in combination therapy with one or more additional agents (e.g., one or more blood modifiers, anti-hypertensive agents, dyslipidemic agents, peptides which mitigates one or more symptoms of atherosclerosis, other agents, including combinations thereof) to prevent or treat vascular conditions and associated thrombotic events as described, for example, in US20020147184. Vascular diseases and conditions are often associated with thrombotic events sometimes resulting in myocardial infarction, stroke and ischemic attack. A thrombotic event is one associated with the formation or presence of a thrombus (e.g., blood clot). Thrombotic events include but are not limited to arterial thrombosis, coronary thrombosis, heart valve thrombosis, coronary stenosis, stent thrombosis and graft thrombosis. Blood clots associated with thrombic events result from an aggregation of blood factors, primarily platelets and fibrin with entrapment of cellular elements

and frequently cause vascular obstruction at the point of their formation. Blood coagulation is a process consisting of a complex interaction of various blood components, or factors, which eventually gives rise to a fibrin clot. It is often desirable to selectively block or inhibit the coagulation cascade in subjects at risk for or exhibiting a vascular disease or condition with blood modifiers e.g., heparin, coumarin, derivatives of coumarin, indandione derivatives, thrombin inhibitors, factor Xa inhibitors, or other agents. For example, in the case of atherosclerosis, proliferation of smooth muscle cells (SMCs) in the vessel wall is an important event in the formation of vascular lesions after vascular reconstruction or in response to other vascular injury. SMC proliferation typically occurs within the first few weeks and up to six months after injury. Thrombosis and or SMC proliferation are also involved in restenosis, which is the re-occlusion of the blood vessel or valve after surgical treatment e.g., angioplasty or bypass grafts. Thus, the compounds and pharmaceutical formulations described herein can be used to prevent or treat restenosis. The compounds and pharmaceutical formulations described herein can also be used to improve coagulation homeostasis (including reducing plasminogen activating inhibitor (PAI)-1 activity, reducing fibrinogen, managing high levels of fibrinogen, promoting fibrinolysis, and/or reducing platelet aggregation, and/or improving endothelial function). The compounds and pharmaceutical formulations described herein can used as coatings on surgical devices (e.g., catheters) and implants (e.g., stents) to reduce the risk of restenosis and thrombosis associated with invasive procedures used in the treatment of cardiovascular diseases.

[0037] The compounds and pharmaceutical formulations described herein can be used alone or in combination therapy with one or more additional agents (e.g., one or more anti-hypertensive agents, dyslipidemic agents, peptides which mitigates one or more symptoms of atherosclerosis, other agents, including combinations thereof) to prevent or treat vascular (e.g., cardiovascular, cerebrovascular, peripheral vascular, renovascular disease, mesenteric vascular, pulmonary vascular disease, ocular vascular) inflammation in a subject in need of such treatment, for example, as described in US20030119757 and to reduce blood plasma or serum concentrations of C-reactive protein (CRP) in a subject in need of such treatment, for example, as

described in US20030119757. Vascular inflammation can lead to atherosclerosis or coronary heart disease. Atherosclerosis is often indicated by a thickening and build-up of plaque in the arteries and typically occurs when the innermost layer of an artery, the endothelium, becomes damaged by cholesterol, toxins, oxidants, infectious agents and the like. The damaged endothelial cells in the artery walls produce adhesion molecules that allow white blood cells to accumulate in the vessel wall. Fats and cholesterol also build-up with the white blood cells causing inflammation of the artery. Such build-up can thicken to a point where the artery becomes vulnerable to blockage from a clot resulting in heart attack or stroke. The compounds and pharmaceutical formulations described herein can be used alone or in combination therapy to slow the progression or cause regression of atherosclerotic plaques or lesions in, for example, coronary arteries, carotid arteries, the peripheral arterial system. Vascular inflammation often precedes the development and the continual process of atherosclerotic coronary heart disease. Vascular inflammation, beginning with an injury or change in the endothelial wall of the artery, may cause an alteration in the intimal layer that increases platelet adhesion to the endothelium. Vascular stimuli to mammals, e.g., cellular injury or inflammation, may lead to the production of various proteins, commonly called acute response proteins, in the body. CRP (C-reactive protein) is an acute response protein. Manufactured in the liver and deposited in damaged tissue, CRP is found in high levels in inflammatory fluids and in both the intimal layer of the atherosclerotic artery and within the lesions of atherosclerotic plaque. Studies have shown a positive association between CRP and coronary artery disease. For example, in a survey of 388 British men aged 50-69, the prevalence of coronary artery disease increased 1.5 fold for each doubling of CRP level (Mendall et al. (1996) BMJ. 312:1061-1065). Multiple prospective studies have also demonstrated that baseline CRP is a good marker of future cardiovascular events (Riker et al. 1998. J Investig Med. 46:391-395). Patients with CRP levels greater than about 0.4 mg/dL have been reported as having increased vascular inflammation and increased risk for vascular disease as compared to patients with levels less than 0.4 mg/dL. (L. Gruberb, "Inflammatory Markers in Acute Coronary Syndromes: C-reactive Protein (CRP) and Chlamydia", American Heart Assoc. Scientific Sessions 2000). Patients with levels

greater 3.4 mg/dL of c-reactive protein were reported to be in the highest quartile of risk. Patients in the second quartile (0.4 to 1.0 mg/dL of c-reactive protein) and third quartile (1.0 to 3.4 mg/dL of c-reactive protein) also have increased risk of vascular disease as compared to patients in the lowest quartile (<0.4 mg/dL c-reactive protein). CRP assays and methodologies for the same are available from Dade Behring Inc., Deerfield, Ill. Methods for analyzing CRPs are described, for example, in US5358852, US6040147, US6277584, and US20030119757.

[0038] The compounds and pharmaceutical formulations described herein can be used alone or in combination therapy with one or more additional agents (e.g., one or more agents used to treat Alzheimer's disease, other agents, including combinations thereof) to prevent, treat, or ameliorate symptoms of Alzheimer's Disease (AD), regulate production or levels of at least one amyloid β (Aβ) peptide and/or regulate the amount of ApoE isoform 4 in the bloodstream and/or brain of a subject, for example, as described in US2003013699 and US6080778. The compositions can be administered to a subject that exhibits no symptoms of AD, has AD, has a family history of AD or dementia illness, is a human, is a human and has trisomy 21 (Down's syndrome), is a human and carries one or more mutations in the genes that encode β amyloid precursor protein (presenilin-1 or presinilin-2), is a human and carries the Apolipoprotein E isoform 4 gene, is a human and is greater than about 40 years of age, is a human and is greater than about 60 years of age. The subject can have an elevated blood cholesterol level, a total serum cholesterol level that is at least about 200 mg/dl, a total low density lipoprotein (LDL) level that is greater than about 100 mg/dl. In some circumstances, the subject has an elevated level of at least one Aβ peptide in the bloodstream and/or brain. In various circumstances, the subject has an elevated level of Aβ-42 in the bloodstream and/or brain, has a level of Aβ-42 peptide greater than about 30 pM in the bloodstream, has a level of Aβ-42 peptide greater than about 40 pM in the bloodstream, has a level of Aβ-42 peptide ranging from about 30 pM to about 80 pM in the bloodstream, has a level Aβ-42 peptide of greater than about 50 pmol/gram of wet brain tissue. In various circumstances, the subject has a level of Aβ-40 peptide greater than about 200 pM in the bloodstream, has a level of Aβ-40 peptide greater than about 400 pM in the bloodstream, has a level of Aβ-40 peptide

ranging from about 200 pM to about 800 pM in the bloodstream, has a level of Aβ-40 peptide greater than about 10 pmol/gram of wet brain tissue. In certain circumstances, the subject's level of Aβ peptide in the bloodstream is reduced from about 10 to about 100 percent from a level of Aβ peptides prior to administration of a composition of the present invention.

[0039] The compounds and pharmaceutical formulations described herein can be used alone or in combination therapy with one or more additional agents (e.g., one or more agents used to treat Alzheimer's disease, other agents, including combinations thereof) to enhance memory or to prevent, treat, or ameliorate symptoms of one or more of dementia, vascular dementia, Huntington's Disease, hydrocephalus, amnesia, AIDs-related dementia, Pick's Disease, Creutzfeldt-Jakob Syndrome, electroconvulsive therapy, Huntington's disease, amyotropic lateral sclerosis, Down syndrome, mental retardation, Parkinson's Disease, mild cognitive impairment, and memory loss.

[0040] The compounds and pharmaceutical formulations described herein can be used alone or in combination therapy with one or more additional agents (e.g., one or more anti-obesity agents, other agents, including combinations thereof) to prevent or treat obesity in a subject in need of such treatment, for examples as described in US20030119428. Obesity is a common medical problem in developed countries and is a risk factor for other illnesses, e.g., hypertension, diabetes, degenerative arthritis and myocardial infarction. Weight loss medications may be appropriate for use in selected patients who are obese or who are overweight with co-morbid conditions. One measure for defining obesity is known as a body mass index (BMI), which is weight in kilograms divided by height in meters squared. A BMI of 18.5 to 24.9 is generally classified as normal, a BMI of 25.0 to 29.9 is generally classified as overweight and a BMI of 30 or greater is generally classified as obese. Alternatively, obesity may be defined as the top percentile, e.g., 15 percent, of a population's weight for a given height. Such definitions of obesity, however, are not a measure of body composition and different people may have higher or lower levels of body fat or muscle mass for their height. Nevertheless, these definitions of obesity are useful characterizations for general populations of people.

[0041] The compounds and pharmaceutical formulations described herein can be used alone or in combination therapy with one or more additional agents to prevent or decrease the incidence of xanthomas in a subject in need of such treatment, for example, as described in US20030119809. Xanthomas are benign fatty tumors associated with the accumulation of fatty materials under the surface of the skin and are often associated with those who have high triglyceride and cholesterol levels. Xanthoma itself may be indicative of an underlying disease e.g., diabetes, primary biliary cirrhosis, some types of cancer, or hypercholesterolemia.

[0042] The compounds and pharmaceutical formulations described herein can be used alone or in combination therapy with one or more additional agents (e.g., one or more anti-hypertensive agents, dyslipidemic agents, peptides which mitigates one or more symptoms of atherosclerosis, other agents, including combinations thereof) to prevent or minimize muscular degeneration and related side effects associated with certain HMG-CoA reductase inhibitors (statins), for example, as described in US20030119808. Muscle degeneration encompasses all side effects relating to muscle degradation, aches, and/or weakness that may be associated with the administration of certain statins, including rhabdomyolysis and/or myopathy. Rhabdomyolysis is the destruction or degeneration of skeletal muscle tissue that is accompanied by the release of muscle cell contents (as myoglobin and potassium) into the bloodstream resulting in hypovolemia, hyperkalemia, and sometimes acute renal failure. Certain statins, allegedly have caused severe muscle degeneration in patients; cerivastatin allegedly has been associated with deaths due to rhabdomyolysis. Myopathies which refer to disorders of muscle tissue or muscles include muscle aches and muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values over ten times the upper limit of normal. Risk of myopathy may be increased during use of high dose statins and/or when statins are administered with other drugs e.g., fibrates, niacin, azole, antifungals, erythromycin, and cyclosporin. The subjects to which the compound or pharmaceutical formulation is administered include those that have or are at risk for a vascular condition, a cardiovascular condition, hypercholesterolemia, atherosclerosis, arteriosclerosis. Suitable subjects include those

having no history of clinically evident heart disease as well as those having a history of clinically evident heart disease.

[0043] The compounds and pharmaceutical formulations described herein can be used alone or in combination therapy with one or more additional agents (e.g., one more anti-diabetic agents, anti-hypertensive agents, dyslipidemic agents, peptides which mitigates one or more symptoms of atherosclerosis, other agents, including combinations thereof) to prevent or treat diabetes and associated conditions in a subject in need of such treatment, for example, as described in US20040214811. Diabetes mellitus, commonly called diabetes, refers to a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose, referred to as hyperglycemia. There are two major forms of diabetes: Type 1 diabetes (also referred to as insulin-dependent diabetes or IDDM) and Type 2 diabetes (also referred to as noninsulin dependent diabetes or NIDDM). Type 1 diabetes is the result of an absolute deficiency of insulin, the hormone that regulates glucose utilization. Type 1 diabetes has two forms: Immune-Mediated Diabetes Mellitus, which results from a cellular mediated autoimmune destruction of the β cells of the pancreas; and Idiopathic Diabetes Mellitus, which refers to forms of the disease that have no known etiologies. Type 2 diabetes is a disease characterized by insulin resistance accompanied by relative, rather than absolute, insulin deficiency. Premature development of atherosclerosis and increased rate of cardiovascular and peripheral vascular diseases are characteristic features of patients with diabetes. Diabetes and associated conditions include but are not limited to Type 1 diabetes, Type 2 diabetes, gestational diabetes mellitus (GDM), maturity onset of diabetes of the young (MODY), pancreatitis, polycystic ovarian disease, impaired glucose tolerance, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, obesity, Syndrome X, dysmetabolic syndrome and related diseases, diabetic complications (including retinopathy, neuropathy, nerphropathy) and sexual dysfunction. The conditions, diseases, and maladies collectively referenced to as "Syndrome X" or Dysmetabolic Syndrome (as detailed in Johanson, J. Clin. Endocrinol. Metab., 1997, 82, 727-734, and other publications) include hyperglycemia and/or prediabetic insulin resistance syndrome, and is characterized by an initial

insulin resistant state generating hyperinsulinemia, dyslipidemia, and impaired glucose tolerance, which can progress to Type II diabetes, characterized by hyperglycemia, which can progress to diabetic complications.

[0044] The compounds and pharmaceutical formulations described herein can be used alone or in combination therapy with one or more additional agents (e.g., one more agents used to treat autoimmune disorders, other agents, including combinations thereof) to prevent or treat at least one autoimmune disorder in a subject in need of such treatment, for example, as described (including the rationale for the therapy) in US20040092499. Autoimmune disorders include, but are not limited to: Alopecia Areata, Ankylosing Spondylitis, Antiphospholipid Syndrome, aplastic anemia, myelodysplastic syndromes, paroxysmal nocturnal hemoglobulinemia, pure red cell aplasia, chronic neutropenias, amegakaryocytic thrombocytopenia, antiphospholipid syndromes, autoimmune thrombocytopenia, autoimmune hemolytic syndromes, antiphospholipid syndromes, autoimmune gastritis, achlorhydria, Autoimmune Addison's Disease, Autoimmune Diabetes, Autoimmune Hemolytic Anemia, Autoimmune Hepatitis, Autoimmune chronic Hepatitis, Autoimmune hypophysitis, Autoimmune orchiditis, autoimmune ovarian failure, Behcet's Disease, Bullous Pemphigoid, Cardiomyopathy, Celiac Sprue-Dermatitis, Cicatrical pemphigoid, Chronic Fatigue Immune Dysfunction Syndrome (CFIDS), Chronic Inflammatory Demyelinating Polyneuropathy, Interstitial cystitis, Churg-Strauss Syndrome, Cicatricial Pemphigoid, CREST Syndrome, Cold Agglutinin Disease, Crohn's Disease, Dermatitis herpetiformis, Discoid Lupus, Drug-induced autoimmune disorders, Endometriosis, Epidermolysis bullosa acquisita, Essential Mixed Cryoglobulinemia, Fibromyalgia-Fibromyositis, Glomerulonephritis, Good Pasture Syndrome, Graft Versus Host Disease, Graves' Disease, Guillain-Barr, Hashimoto's Thyroiditis, Idiopathic Inflammatory Myopathies, Idiopathic Pulmonary Fibrosis, Idiopathic Thrombocytopenia Purpura (ITP), IgA Nephropathy, Insulin Dependent Diabetes, Juvenile Arthritis, Lichen Planus, Systemic Lupus Erythmatosus, Mnire's Disease, Metal-induced autoimmunity disorders, Mixed Connective Tissue Disease, Multiple Sclerosis, Myasthenia Gravis, Myocarditis, Myositis, Optic neuritis, Painless/postpartum thyroiditis, Peripheral nerve vasculitis, Pemphigus Foliaceus,

Pemphigus Vulgaris, Pernicious Anemia, Polyarteritis Nodosa, Polychondritis, Polyglandular Syndromes, Polymyalgia Rheumatica, Polymyositis and Dermatomyositis, Postinfectious autoimmune disorders, Primary Agammaglobulinemia, Primary Biliary Cirrhosis, Psoriasis, Psoriatic Arthritis, Reactive Arthritis, Raynaud's Phenomenon, Reiter's Syndrome, Rheumatic Fever, Rheumatoid Arthritis, Sarcoidosis, Scleritis, Scleroderma, Sjogren's Syndrome, Stiff-Man Syndrome, Takayasu Arteritis, Temporal Arteritis/Giant-cell Arteritis, Ulcerative Colitis, Uveitis, Vasculitis, Vitiligo, Kawasaki Disease, and Wegener's Granulomatosis.

[0045] The compounds and pharmaceutical formulations described herein can be used alone or in combination therapy with one or more additional agents (e.g., one more agents used to treat demylenation and its associated disorders, other agents, including combinations thereof) to prevent or treat demyelination and associated disorders in a subject in need of such treatment, for example, as described (including the rationale for the therapy) in US20040092500. Nerve fibers are wrapped with multiple layers of insulation known as myelin sheath. Demyelination can occur through disease and results in the destruction or removal of the myelin sheath. Primary demyelinating disorders include but are not limited to multiple sclerosis, acute disseminated encephalomyelitis, adrenoleukodystrophy, adrenomyeloneuropathy, Leber's hereditary optic atrophy and HTLV-associated myelopathy. Other disorders associated with demyelination include but are not limited to Tay-Sachs disease, Niemann-Pick disease, Gaucher's disease and Hurler's syndrome; or stroke, inflammation, immune diseases, metabolic disorders, poison or drugs.

[0046] The compounds and pharmaceutical formulations described herein can be used alone or in combination therapy with one or more additional agents (e.g., one or more chemotherapeutic agents, anti-cancer agents, other agents, including combinations thereof) to prevent or treat cholesterol associated tumors in patients who are either at risk of developing a cholesterol-associated tumor or already exhibit a cholesterol associated tumor, for example, as described in US20040116358. The compounds of the invention may reduce both cholesterol levels in vivo and

epoxycholesterol formation and thereby inhibit initiation and progression of benign and malignant cholesterol-associated tumors or cholesterol-associated cell growth or cell-masses. The tumors may be benign cholesterol-associated tumors or cholesterol-associated cell growth or cell-masses including but not limited to benign tumors associated with prostate, colon, endometrial, or breast tissues or prostate, colon, breast, or endometrial cancer. Thus the compounds and pharmaceutical formulations described herein, for example, are useful to prevent or treat benign prostatic hypertrophy. The tumors may be malignant cholesterol-associated tumors or cholesterol-associated cell growth or cell-masses including but not limited to malignant tumors associated with prostate, colon, endometrial, or breast tissues or prostate, colon, breast, or endometrial cancer.

[0047] The compounds and pharmaceutical formulations described herein can be used alone or in combination therapy with one or more additional agents (e.g., one or more chemotherapeutic agents, anti-cancer agents, other agents, including combinations thereof) for one or more of: inhibiting the expression of at least one multiple ("multi")-drug resistance gene or protein in an animal cell, enhancing the effectiveness of a chemotherapeutic agent in an animal having cancer, and reversing a multi-drug resistance phenotype exhibited by an animal cell all of which are, for example, described in WO05/030225. Co-administration (though not necessarily concurrent or proximal consecutive) of cholesterol absorption inhibitors and chemotherapeutic agents can inhibit the expression of multi-drug resistance genes. Thus the compounds and pharmaceutical formulations described herein can be used alone or in combination therapy in one or more of: a) treating or alleviating a cancer; b) preventing, treating or alleviating tumour growth; c) inhibiting or reducing the expression of one or more multiple drug resistance genes; d) inhibiting or reducing the production of one or more proteins expressed by multiple drug resistance genes; e) enhancing the effectiveness of a chemotherapeutic agent in treating a cancer; and f) sensitizing a cell to one or more chemotherapeutic agents. Multiple drug resistance genes include but are not limited to ABCB1 (MDR-1), ABCA2 (ABC2), ABCB2 (TAP), ABCB3 (TAP), ABCC1 (MRP-1), and ABCC3 (MRP-3).

[0048] The compounds and pharmaceutical formulations described herein can be used alone or in combination therapy with one or more additional agents (e.g., dyslipidemic agents, anti-diabetic agents, anti-hypertensive agents, anti-obesity agents, agents used to treat autoimmune disorders, agents used to treat demylenation and its associated disorders, agents used to treat Alzheimer's disease, blood modifiers, hormone replacement agent/compositions, chemotherapeutic agents, peptides which mitigate one or more symptoms of atherosclerosis, anti-cancer agents, agents used to treat bone loss and associated disorders, other agents, including combinations therof) to modulate lipid raft structure (for example by reducing the level of cholesterol in the lipid raft), for example, as described (including the related rationale) in WO05023305. Lipid rafts are discrete microdomains in the plasma membrane which are rich in sphingolipids and contain ordered cholesterol (Field et al., J. Biol. Chem., 1997,272, 4276-4280). In a number of cells, it has become clear that certain membrane associated proteins preferentially partition into these lipid rafts (Foster, de Hoog and Mann, PNAS, 2003,100, 5813-8). These include various seven transmembrane domain receptors and their associated G proteins and various proteins that are attached to the inner membrane leaflet through lipid moieties such as prenylation, including small molecular weight G proteins, such as Ras, Rac, cdc42 and Rho. Disruption of lipid rafts results in an uncoupling of efficient signal transduction through receptors such as G protein coupled receptors, the T cell receptor and the high affinity IgE receptor. Compounds which modulate lipid raft structure may be useful in the treatment or prophylaxis of a wide variety of diseases and conditions. The compounds and pharmaceutical formulations described herein can be used alone or in combination therapy to prevent or treat a disease or condition associated with lipid raft structure such as respiratory tract/obstructive airways diseases and disorders (including: acute-, allergic, hatrophic rhinitis or chronic rhinitis (such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca), rhinitis medicamentosa, membranous rhinitis (including croupous, fibrinous and pseudomembranous rhinitis), scrofulous rhinitis, perennial allergic rhinitis, seasonal rhinitis (including rhinitis nervosa (hay fever) and vasomotor rhinitis), antitussive activity, asthma (such as bronchial, allergic, intrinsic, extrinsic and dust asthma particularly chronic or inveterate asthma (e.g., late

asthma and airways hyper-responsiveness)), bronchitis (including chronic and eosinophilic bronchitis), emphysema, chronic inflammatory diseases of the lung which result in interstitial fibrosis, such as interstitial lung diseases (ILD) (e.g., idiopathic pulmonary fibrosis, or ILD associated with rheumatoid arthritis, or other autoimmune conditions), chronic obstructive pulmonary disease (COPD)(such as irreversible COPD), chronic sinusitis, conjunctivitis (e.g., allergic conjunctivitis), cystic fibrosis, fanner's lung and related diseases, fibroid lung, hypersensitivity lung diseases, hypersensitivity pneumonitis, idiopathic interstitial pneumonia, nasal congestion, nasal polyposis, otitis media, and chronic cough associated with inflammation or iatrogenic induced); systemic anaphylaxis or hypersensitivity responses (such as drug allergies (e.g., to penicillin, cephalosporins), insect sting allergies, pet allergies, house dust mite allergies, pollen allergies, and food related allergies which may have effects remote from the gut (such as migraine, rhinitis and eczema)); gastro-intestinal diseases and disorders (such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, gastric and duodenal ulceration), Fabry's disease; Kimura's disease; multiple sclerosis; wound healing; liver hepatitis and cirrhosis; rheumatoid arthritis; juvenile rheumatoid arthritis; systemic lupus erythematosus; degenerative joint disease; connective tissue diseases; ankylosing spondylitis; soft tissue rheumatism (e.g., tendonitis, bursitis); Sjogren's syndrome; psoriasis; psoriatic arthritis; neuralgia; synovitis; glomerulonephritis; vasculitis; sacoidosis; inflammations that occur as sequellae to influenza; the common cold and other viral infections; gout; pseudogout; contact dermatitis; low back and neck pain; dysmenorrhea; headache; dementias; toothache; sprains; strains; myositis; burns; injuries; pain and inflammation that follows surgical and dental procedures in a patient; Parkinsons disease; muscular dystrophy; neoplasia; hyperparathyroidism; sepsis and septic shock; infections by intracellular pathogens (including, for example, bacteria (such as Salmonella, Chlamydiae, listeria, Mycobacteria tuberculosis), viruses (such as HIV, Measles virus, Papilloma viruses, Epstein-Barr virus, Respiratory Syncytial Virus (RSV), Hepatitis, Herpes viruses, Influenza virus, Ebola and Marburg viruses), parasites (such as Plasmodium (malaria), leishmania, Trypanosoma (sleeping sickness), Toxoplasma gondii)); and bacterial

infections including Shigella, Escherichia Coli (including 0157), Campylobacter, Vibrio cholerae, Clostridium difficile and Clostridium tetani.

[0049] The compounds and pharmaceutical formulations described herein can be used alone or in combination therapy with one or more additional agents (e.g., one or more dyslipidemic agents, peptides which mitigates one or more symptoms of atherosclerosis, hormone replacement agents/compositions, anti-cancer agents, chemotherapeutic agents, agents used to treat bone loss and associated disorders, other agents, including combinations thereof) to prevent or treat osteopenia disorders (bone loss disorders) in subjects in need of such treatment. There is a well documented co-morbid development of bone loss disorders (e.g., osteoporosis) and cardiovascular disease. For example, Gas-6, osteocalcin, matrix gammacarboxy glutamate protein and protein S function in both bone formation and arterial calcification. Bone loss disorders and associated conditions include but are not limited to: osteoporosis, Paget's disease (osteitis deformans), bone loss, bone fractures, bone segmental defects, abnormally increased bone turnover, conditions associated with bone fracture or deficiency, rheumatoid arthritis (including bone loss attendant rheumatoid arthritis), osteoarthritis, osteolysis (including familial expansile osteolysis and periprostetic osteolysis), osteolytic metastases, osteolytic bone disease, metastatic bone disease, osteosarcoma, osteonecrosis, osteogenesis imperfecta, osteomyelitis (e.g., an infectious lesion in bone leading to bone loss), cleiodocranial dysplasia (CCD), prosthetic loosening, periodontal disease (e.g., periodontitis) and defects, and other tooth repair processes, tooth loss, primary or secondary hyparathyroidism, hypercalcemia (including hypercalcemia of malignancy, and multiple myeloma), cartilage defects or disorders (including cartilage degeneration), conditions associated with connective tissue repair (e.g., healing or regeneration of cartilage defects or injury), metabolic bone diseases, and transplant and drug-induced bone loss. Osteoporosis includes primary osteoporosis, secondary osteoporosis, medication-induced osteoporosis (e.g., corticosteroid-induced osteoporosis, transplant-bone disease), age-related osteoporosis in females or males, post-menopausal osteoporosis, glucocorticoid-induced osteoporosis, idiopathic osteoporosis, disease-induced arthritis (e.g., rheumatoid arthritis induced), disuse osteoporosis and arthritis, diabetes-related

osteoporosis, endocrine osteoporosis (hyperthyroidism, hyperparathyroidism, Cushing's syndrome, and acromegaly), hereditary and congenital forms of osteoporosis (osteogenesis imperfecta, homocystinuria, Menkes' syndrome, and Rile-Day syndrome) and osteoporosis due to immobilization of extremities. The compounds and pharmaceutical formulations described herein can be used alone or in combination therapy in one more of the following: enhancing/promoting bone formation; preventing bone loss; repair of bone defects and deficiencies, such as those occurring in closed, open and nonunion fractures; prophylactic use in closed and open fracture reduction; promotion of bone healing in plastic surgery; stimulation of bone ingrowth into non-cemented prosthetic joints and dental implants; elevation of peak bone mass in perimenopausal women; prevention or treatment of growth deficiencies; prevention or treatment of increased bone formation during distraction osteogenesis; prevention or treatment of any condition that benefits from stimulation of bone formation; repair of congenital, trauma-induced or surgical resection of bone (for instance, for cancer treatment), and in cosmetic surgery; treatment of wound healing or tissue repair; treatment of subjects undergoing facial reconstruction surgery; treatment of subjects undergoing orthopedic or oral surgery; alleviation of bone pain; prevention or treatment of localized bone loss associated with periprosthetic osteolysis and bone fractures, etc.; rapid inhibition of bone resorption in a subject while obtaining a rapid reduction of bone turnover and biomarkers; rapid increase of bone mineral density; and rapid reduction of fractures. The compounds and pharmaceutical formulations described herein can be used alone or in combination therapy to stimulate bone regeneration. The bone regeneration may be following reconstruction of bone defects in cranio-maxillofacial surgery, or following an implant into bone, for example a dental implant, bone supporting implant, or prosthesis. The bone regeneration may also be following a bone fracture.

[0050] The compounds and pharmaceutical formulations described herein can be used alone or in combination therapy with one or more additional agents for preventing and treating malignant lesions (such as ductal carcinoma in situ of the breast and lobular carcinoma in situ of the breast), premalignant lesions (such as fibroadenoma of the breast and prostatic intraepithelial neoplasia (PIN),

gastrointestinal malignancies, liposarcomas and various other epithelial tumors (including breast, prostate, colon, ovarian, gastric and lung), cancer-induced asthenia (fatigue), irritable bowel syndrome, Crohn's disease, gastric ulceritis, and gallstones, and HIV infection, other infectious diseases, drug-induced lipodystrophy, and proliferative diseases such as psoriasis, for example, as described in US20050085497.

[0051] As described, for example, in US20050101565, the compounds and pharmaceutical formulations described herein can be used alone or in combination therapy with one or more additional agents to prevent or treat: cancers (including but not limited to human sarcomas and carcinomas, e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma; leukemias, e.g., acute lymphocytic leukemia and acute myelocytic leukemia (myeloblastic, promyelocytic, myelomonocytic, monocytic and erythroleukemia); chronic leukemia (chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia); and polycythemia vera, lymphoma (Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, and heavy chain disease (In certain embodiments, the cancers that are treated or prevented by administering the compounds described herein are insulin resistance or Syndrome X related cancers, including but not limited to breast, prostate and colon cancer); PPAR-associated disorders (including but not limited to rheumatoid arthritis; multiple sclerosis; psoriasis; inflammatory bowel diseases; breast; colon or prostate

cancer; low levels of blood HDL (HDL may be elevated in lymph and/or cerebral fluid); low levels of blood, lymph and/or cerebrospinal fluid apo E; low blood, lymph and/or cerebrospinal fluid levels of apo A-I; high levels of blood VLDL; high levels of blood LDL; high levels of blood triglyceride; high levels of blood apo B; high levels of blood apo C-III and reduced ratio of post-heparin hepatic lipase to lipoprotein lipase activity; renal diseases including but not limited to glomerular diseases (including but not limited to acute and chronic glomerulonephritis, rapidly progressive glomerulonephritis, nephrotic syndrome, focal proliferative glomerulonephritis, glomerular lesions associated with systemic disease, such as systemic lupus erythematosus, Goodpasture's syndrome, multiple myeloma, diabetes, neoplasia, sickle cell disease, and chronic inflammatory diseases), tubular diseases (including but not limited to acute tubular necrosis and acute renal failure, polycystic renal disease, medullary sponge kidney, medullary cystic disease, nephrogenic diabetes, and renal tubular acidosis), tubulointerstitial diseases (including but not limited to pyelonephritis, drug and toxin induced tubulointerstitial nephritis, hypercalcemic nephropathy, and hypokalemic nephropathy), acute and rapidly progressive renal failure, chronic renal failure, nephrolithiasis, or tumors (including but not limited to renal cell carcinoma and nephroblastoma) (In certain embodiments, renal diseases that are treated by the compounds described herein are vascular diseases, including but not limited to hypertension, nephrosclerosis, microangiopathic hemolytic anemia, atheroembolic renal disease, diffuse cortical necrosis, and renal infarcts); and septicemia and impotence (for example, which may result from cardiovascular disease).

[0052] In addition to the other subjects discussed herein, the compositions and pharmaceutical formulations described herein can be administered alone or in combination therapy with one or more additional agents (e.g., one or more hormone replacement agents/compositions, dyslipidemic agents, peptides which mitigates one or more symptoms of atherosclerosis, anti-hypertensive agents, anti-diabetic agents, anti-obesity agents, other agents, including combinations thereof) to post-menopausal women, for example, as described in US20030119796. In various embodiments, the compositions and pharmaceutical formulations described herein can be administered

alone or in combination therapy with one or more additional agents to, for example, (1) a subject in need of or who has undergone an organ transplant (e.g., a kidney transplant), (2) a subject who is either at risk of developing systemic lupus erythematosus or already exhibits systemic lupus erythematosus, (3) a subject who has undergone or is undergoing hemodialysis, (4) a subject who is either at risk of developing hyperhomocysteine levels or already exhibits hyperhomocysteine levels, (5) a subject who is either at risk of developing hypothyroidism or already exhibits hypothyroidism, (6) a subject who is either at risk of developing obstructive liver disease or already exhibits obstructive liver disease, (7) a subject who is either at risk of developing kidney disease or already exhibits kidney disease, (8) a subject who has undergone cardiac bypass surgery, and (9) a subject who has undergone percutaneous transluminal coronary angioplasty.

[0053] The compounds and pharmaceutical formulations described herein can be administered alone or in combination therapy with one or more additional agents to a non-human animal for a veterinary use for treating, preventing, or managing a disease or disorder disclosed herein. Non limiting examples of non-human examples include cows, horses, sheep, pigs, cats, dog, mice, rats, rabbits, guinea pigs, and fowl species (e.g., chicken, turkey, duck, goose, quail). In addition to veterinary uses, the compounds and pharmaceutical formulations described herein can be used to reduce the fat content of livestock to produce leaner meats and to reduce the cholesterol content of eggs by administering the compounds to a chicken, quail, or duck hen. For non-human animal uses, the compounds and pharmaceutical formulations described herein can be administered via the animals' feed or orally as a drench composition.

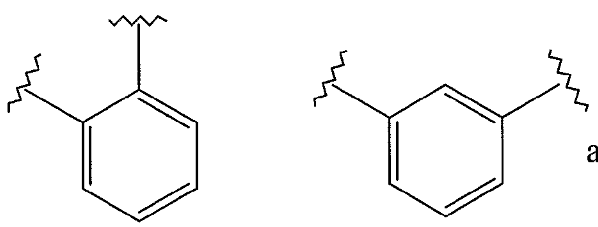
[0054] Certain compounds of the invention may have the additional advantage that they suppress serum cholesterol and/or LDL levels while themselves not being appreciably absorbed into the mammalian circulation upon oral administration. As a result of the low-to-insignificant serum levels, fewer side-effects, such as drug-drug interactions, are observed.

Definitions

[0055] Throughout this specification the terms and substituents retain their definitions.

[0056] Alkyl is intended to include linear, branched, or cyclic hydrocarbon structures and combinations thereof. When not otherwise restricted, the term refers to alkyl of 20 or fewer carbons. Lower alkyl refers to alkyl groups of 1, 2, 3, 4, 5 and 6 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, s-and t-butyl and the like. Methyl is preferred. Preferred alkyl and alkylene groups are those of C_{20} or below (e.g. C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, C_{20}). Cycloalkyl is a subset of alkyl and includes cyclic hydrocarbon groups of 3, 4, 5, 6, 7, and 8 carbon atoms. Examples of cycloalkyl groups include c-propyl, c-butyl, c-pentyl, norbornyl, adamantyl and the like.

[0057] C_1 to C_{20} Hydrocarbon (e.g. C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, C_{20}) includes alkyl, cycloalkyl, alkenyl, alkynyl, aryl and combinations thereof. Examples include benzyl, phenethyl, cyclohexylmethyl, camphoryl and naphthylethyl. The term "phenylene" refers to ortho, meta or para residues of the formulae:



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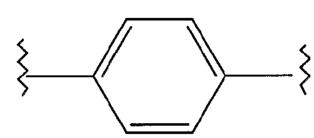


[0058] Alkoxy or alkoxyl refers to groups of 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of a straight, branched, cyclic configuration and combinations thereof attached to the parent structure through an oxygen. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like. Lower-alkoxy refers to groups containing one to four carbons. Methoxy is preferred.

[0059] Oxaalkyl refers to alkyl residues in which one or more carbons (and their associated hydrogens) have been replaced by oxygen. Examples include methoxypropoxy, 3,6,9-trioxadecyl and the like. The term oxaalkyl is intended as it is

understood in the art [see Naming and Indexing of Chemical Substances for Chemical Abstracts, published by the American Chemical Society, ¶196, but without the restriction of ¶127(a)], i.e. it refers to compounds in which the oxygen is bonded via a single bond to its adjacent atoms (forming ether bonds). Similarly, thiaalkyl and azaalkyl refer to alkyl residues in which one or more carbons have been replaced by sulfur or nitrogen, respectively. Examples include ethylaminoethyl and methylthiopropyl.

[0060] Polyol refers to a compound or residue having a plurality of -OH groups. Polyols may be thought of as alkyls in which a plurality of C-H bonds have been replaced by C-OH bonds. Common polyol compounds include for example glycerol, erythritol, sorbitol, xylitol, mannitol and inositol. Linear polyol residues will generally be of the empirical formula $-C_yH_{2y+1}O_y$, and cyclic polyol residues will generally be of the formula $-C_yH_{2y-1}O_y$. Those in which y is 3, 4, 5 and 6 are preferred. Cyclic polyols also include reduced sugars, such as glucitol.

[0061] Acyl refers to groups of 1, 2, 3, 4, 5, 6, 7 and 8 carbon atoms of a straight, branched, cyclic configuration, saturated, unsaturated and aromatic and combinations thereof, attached to the parent structure through a carbonyl functionality. One or more carbons in the acyl residue may be replaced by nitrogen, oxygen or sulfur as long as the point of attachment to the parent remains at the carbonyl. Examples include formyl, acetyl, propionyl, isobutyryl, t-butoxycarbonyl, benzoyl, benzyloxycarbonyl and the like. Lower-acyl refers to groups containing one to four carbons.

[0062] Aryl and heteroaryl refer to aromatic or heteroaromatic rings, respectively, as substituents. Heteroaryl contains one, two or three heteroatoms selected from O, N, or S. Both refer to monocyclic 5- or 6-membered aromatic or heteroaromatic rings, bicyclic 9- or 10-membered aromatic or heteroaromatic rings and tricyclic 13- or 14-membered aromatic or heteroaromatic rings. Aromatic 6, 7, 8, 9, 10, 11, 12, 13 and 14-membered carbocyclic rings include, e.g., benzene, naphthalene, indane, tetralin, and fluorene and the 5, 6, 7, 8, 9 and 10-membered aromatic heterocyclic rings include, e.g., imidazole, pyridine, indole, thiophene, benzopyranone, thiazole, furan, benzimidazole, quinoline, isoquinoline, quinoxaline, pyrimidine, pyrazine, tetrazole and pyrazole.

[0063] Arylalkyl means an alkyl residue attached to an aryl ring. Examples are benzyl, phenethyl and the like.

[0064] Substituted alkyl, aryl, cycloalkyl, heterocyclyl etc. refer to alkyl, aryl, cycloalkyl, or heterocyclyl wherein up to three H atoms in each residue are replaced with halogen, haloalkyl, hydroxy, loweralkoxy, carboxy, carboalkoxy (also referred to as alkoxycarbonyl), carboxamido (also referred to as alkylaminocarbonyl), cyano, carbonyl, nitro, amino, alkylamino, dialkylamino, mercapto, alkylthio, sulfoxide, sulfone, acylamino, amidino, phenyl, benzyl, heteroaryl, phenoxy, benzyloxy, or heteroaryloxy.

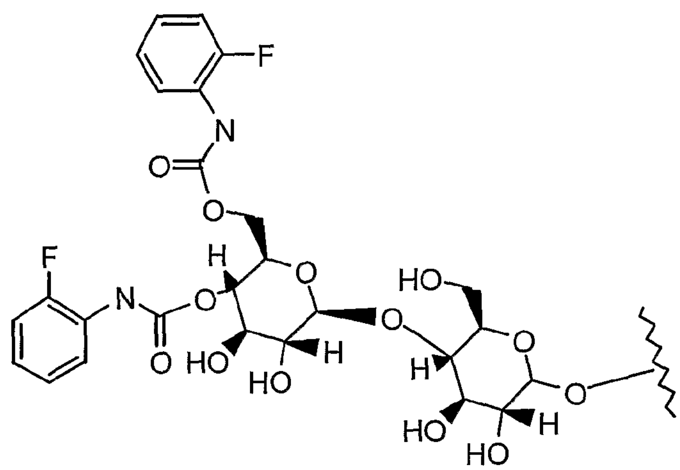
[0065] The term "halogen" means fluorine, chlorine, bromine or iodine.

[0066] The term "sugar" is used in its normal sense, as defined in Hawley's Condensed Chemical Dictionary, 12th Edition, Richard J. Lewis, Sr.; Van Nostrand Reinhold Co. New York. It encompasses any carbohydrate comprised of one or two saccharose groups. The monosaccharide sugars (often called simple sugars) are composed of chains of 2-7 carbon atoms. One of the carbons carries aldehydic or ketonic oxygen, which may be combined in acetal or ketal forms. The remaining carbons usually have hydrogen atoms and hydroxyl groups (or protecting groups for hydroxyl, such as acetate). Among monosaccharides which would be considered within the term "sugars" as intended in this application, are arabinose, ribose, xylose, ribulose, xylulose, deoxyribose, galactose, glucose, mannose, fructose, sorbose, tagatose, fucose, quinovose, rhamnose, manno-heptulose and sedoheptulose. Among the disaccharides are sucrose, lactose, maltose, and cellobiose. Unless specifically modified, the general term "sugar" refers to both D-sugars and L-sugars. The sugar may also be protected. The sugar may be attached through oxygen (as in US patent 5,756,470) or through carbon (as in PCT WO 2002066464), the disclosures of both of which are incorporated herein by reference.

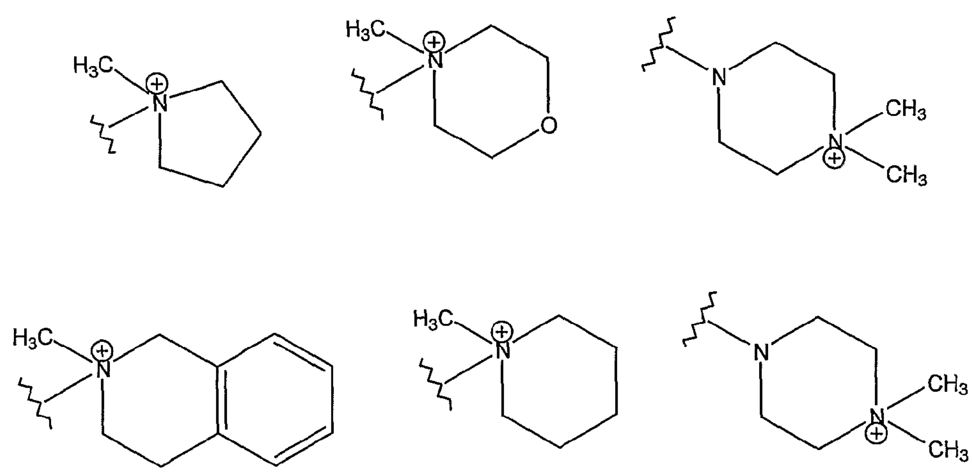
[0067] Reduced C-attached sugars or C-glycosyl compounds are also encompassed by the invention. The reduced sugars (e.g. glucitol), which could be classed either as polyols or as sugars, are also known as alditols. Alditols are polyols having the general formula HOCH2[CH(OH)] nCH2OH (formally derivable from an aldose by reduction of the carbonyl group.

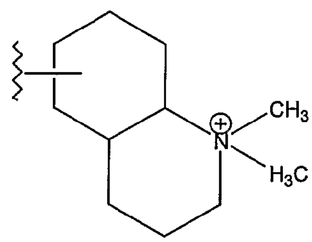
[0068] The term "glucuronide" is also used in its normal sense to refer to a glycoside of glucuronic acid.

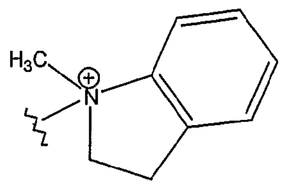
[0069] The term "sugar carbamate" refers to mono-, di- and oligosaccharides in which one or more hydroxyls have been derivatized as carbamates, particularly as phenyl carbamates and substituted phenyl carbamates. [See Detmers et al. Biochim Biophys. Acta 1486, 243-252 (2000), which is incorporated herein by reference.] A preferred sugar carbamate is:

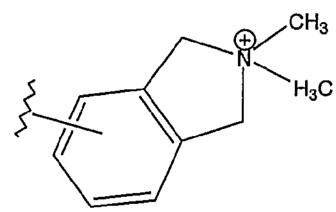


[0070] Examples of quats that fall within the definition of monocyclic and bicyclic trialkylammoniumalkyl residues include:

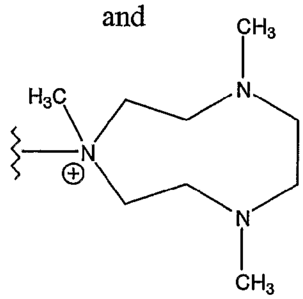








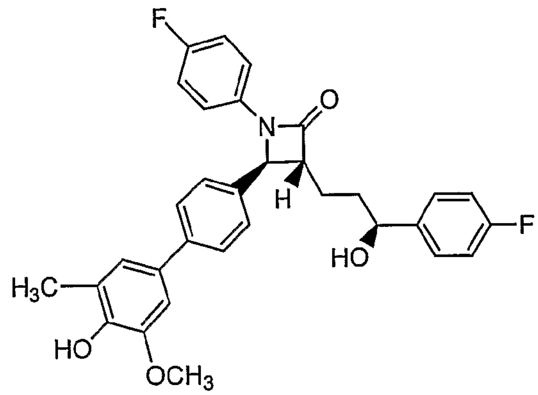
and



[0071] The term "prodrug" refers to a compound that is made more active in vivo. Commonly the conversion of prodrug to drug occurs by enzymatic processes in the liver or blood of the mammal. Many of the compounds of the invention may be chemically modified without absorption into the systemic circulation, and in those cases, activation in vivo may come about by chemical action (as in the acid-catalyzed cleavage in the stomach) or through the intermediacy of enzymes and microflora in the gastrointestinal GI tract.

[0072] In the characterization of the variables, it is recited that R^9 may form a five- to seven-membered ring with A or R^{10}; that R^{10} may form a double bond with A or may form a five- to seven-membered ring with R^9; and that R^{11} may form a second five- to seven-membered ring. It is intended that these rings may exhibit various degrees of unsaturation (from fully saturated to aromatic), may include heteroatoms and may be substituted with lower alkyl or alkoxy.

[0073] In the characterization of the variables, it is recited that R-groups, such as R^5, represent one, two, three, four or five residues chosen independently from a list of variable definitions. The structure below illustrates the intent of that language. In this example, R^5 represents three residues: $-CH_3$, $-OH$ and $-OCH_3$.



[0074] The variables are defined when introduced and retain that definition throughout. Thus, for example, R^3 is always chosen from H, -OH, fluoro, -O-loweralkyl and -O-acyl, although, according to standard patent practice, in dependent claims it may be restricted to a subset of these values. Superscripts are added to distinguish among residues that are attached similarly and that have overlapping Markush groups. For example, the substituent attached to the phenyl ring at the 1-position (i.e. on the nitrogen) of the azetidinone is always labeled R^1, but can be R^1, R^{1a}, R^{1b} or R^{1c} depending on the members of the Markush group defining it. For simplicity, the dependent claims, when multiply dependent, may refer to R^1 etc. This is intended to modify the appropriate value of the corresponding variable R^1, R^{1a}, R^{1b}, R^{1c} etc. in each claim from which it depends. Thus a claim that recites "a compound according to any of claims 1 to 8 wherein R^1 is chosen from H, halogen, -OH and methoxy" intends to further limit, for example, the corresponding R^{1a} substituent in claim 6, the R^{1b} substituent in claim 7 and the R^{1c} substituent in claim 8.

[0075] It will be recognized that the compounds of this invention can exist in forms in which one isotope of a particular atom may be replaced with a different isotope of that same atom. For example, "hydrogen" may be ^{1}H, ^{2}H or ^{3}H; "carbon" may be ^{12}C, ^{13}C, or ^{14}C; "nitrogen" may be ^{14}N or ^{15}N; "oxygen" may be ^{16}O, ^{17}O or ^{18}O; and the like. It will be recognized that the compounds of this invention can exist in radiolabeled form, i.e., the compounds may contain one or more atoms containing an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Radioisotopes of hydrogen, carbon, phosphorous, fluorine, iodine and chlorine include ^{3}H, ^{14}C, ^{35}S, ^{18}F, ^{32}P, ^{33}P, ^{125}I, and ^{36}Cl, respectively. Compounds that contain those radioisotopes and/or other radioisotopes of other atoms

are within the scope of this invention. Tritiated, i.e. ^{3}H, and carbon-14, i.e., ^{14}C, radioisotopes are particularly preferred for their ease in preparation and detectability. Radiolabeled compounds of Formulae I-V of this invention and prodrugs thereof can generally be prepared by methods well known to those skilled in the art. Conveniently, such radiolabeled compounds can be prepared by carrying out the procedures disclosed in the Examples and Schemes by substituting a readily available radiolabeled reagent for a non-radiolabeled reagent.

[0076] The compounds of the invention can also exist in other labeled forms. US20020009714 discloses methods of labeling and uses of labeled cholesterol absorption inhibitors. The labels can be primary labels (where the label comprises an element which is detected directly) or secondary labels (where the detected label binds to a primary label, e.g., as is common in immunological labeling). An introduction to labels, labeling procedures and detection of labels is found in Introduction to Immunocytochemistry, (2d ed.) Polak and Van Noorden,, Springer Verlag, N.Y. (1997) and in Handbook of Fluorescent Probes and Research Chemicals, Haugland (1996), a combined handbook and catalogue published by Molecular Probes, Inc., Eugene, Oreg. Primary and secondary labels can include undetected elements as well as detected elements. Useful primary and secondary labels in the present invention can include spectral labels, which include fluorescent labels such as fluorescent dyes (e.g., fluorescein and derivatives such as fluorescein isothiocyanate (FITC) and Oregon Green™, rhodamine and derivatives (e.g., Texas red, tetramethylrhodamine isothiocyanate (TRITC), etc.), digoxigenin, biotin, phycoerythrin, AMCA, CyDyes™ and the like), radiolabels (including those described above), enzymes (e.g., horseradish peroxidase, alkaline phosphatase etc.) spectral colorimetric labels such as colloidal gold or colored glass or plastic (e.g. polystyrene, polypropylene, latex, etc.) beads. The label may be coupled directly or indirectly to the compound of the invention according to methods well known in the art. As indicated above, a wide variety of labels may be used, with the choice of label depending on sensitivity required, ease of conjugation with the compound, stability requirements, available instrumentation, and disposal provisions. In general, a detector which monitors a protein/inhibitory agent interaction is adapted to the particular label which is used.

Typical detectors include spectrophotometers, phototubes and photodiodes, microscopes, scintillation counters, cameras, film and the like, as well as combinations thereof. Examples of suitable detectors are widely available from a variety of commercial sources known to persons of skill.

[0077] Nonlimiting examples of labels include those which utilize 1) chemiluminescence (using horseradish peroxidase or alkaline phosphatase with substrates that produce photons as breakdown products) with kits being available, e.g., from Molecular Probes, Amersham, Boehringer-Mannheim, and Life Technologies/Gibco BRL; 2) color production (using both horseradish peroxidase or alkaline phosphatase with substrates that produce a colored precipitate) (kits available from Life Technologies/Gibco BRL, and Boehringer-Mannheim); 3) fluorescence (e.g., using Cy-5 (Amersham), fluorescein, and other fluorescent tags); 5) radioactivity. Other methods for labeling and detection will be readily apparent to one skilled in the art.

[0078] In one embodiment, the label is a fluorescent label. Fluorescent labels have the advantage of requiring fewer precautions in handling, and being amendable to high-throughput visualization techniques (optical analysis including digitization of the image for analysis in an integrated system comprising a computer). Preferred labels are typically characterized by one or more of the following: high sensitivity, high stability, low background, low environmental sensitivity and high specificity in labeling. Fluorescent moieties, which are incorporated into the labels of the invention, are generally are known, including Texas red, digoxigenin, biotin, 1- and 2-aminonaphthalene, p,p'-diaminostilbenes, pyrenes, quaternary phenanthridine salts, 9-aminoacridines, p,p'-diaminobenzophenone imines, anthracenes, oxacarbocyanine, merocyanine, 3-aminoequilenin, perylene, bis-benzoxazole, bis-p-oxazolyl benzene, 1,2-benzophenazin, retinol, bis-3-aminopyridinium salts, hellebrigenin, tetracycline, sterophenol, benzimidazolylphenylamine, 2-oxo-3-chromen, indole, xanthen, 7-hydroxycoumarin, phenoxazine, calicylate, strophanthidin, porphyrins, triarylmethanes, flavin and many others. Many fluorescent tags are commercially available from the SIGMA chemical company (Saint Louis, Mo.), Molecular Probes, R&D systems (Minneapolis, Minn.), Pharmacia LKB Biotechnology (Piscataway,

N.J.), CLONTECH Laboratories, Inc. (Palo Alto, Calif.), Chem Genes Corp., Aldrich Chemical Company (Milwaukee, Wis.), Glen Research, Inc., GIBCO BRL Life Technologies, Inc. (Gaithersberg, Md.), Fluka ChemicaBiochemika Analytika (Fluka Chemie AG, Buchs, Switzerland), and Applied Biosystems (Foster City, Calif.), as well as many other commercial sources known to one of skill.

[0079] The labels may be covalently bound to the compounds of the invention by a tether group. The tether group can be any moiety capable of covalently linking to the inhibitors and to the labels. Preferred groups are substituted or unsusbstituted alkylene, alkenylene or alkynylene of 1 to 10 carbon atoms, more preferably 1 to 4 carbon atoms. Particularly preferred groups are unsusbstituted alkynylenes.

[0080] The terms "methods of treating or preventing" mean amelioration, prevention or relief from the symptoms and/or effects associated with lipid disorders. The term "preventing" as used herein refers to administering a medicament beforehand to forestall or obtund an acute episode or, in the case of a chronic condition to diminish the likelihood or seriousness of the condition. The person of ordinary skill in the medical art (to which the present method claims are directed) recognizes that the term "prevent" is not an absolute term. In the medical art it is understood to refer to the prophylactic administration of a drug to substantially diminish the likelihood or seriousness of a condition, and this is the sense intended in applicants' claims. As used herein, reference to "treatment" of a patient is intended to include prophylaxis.

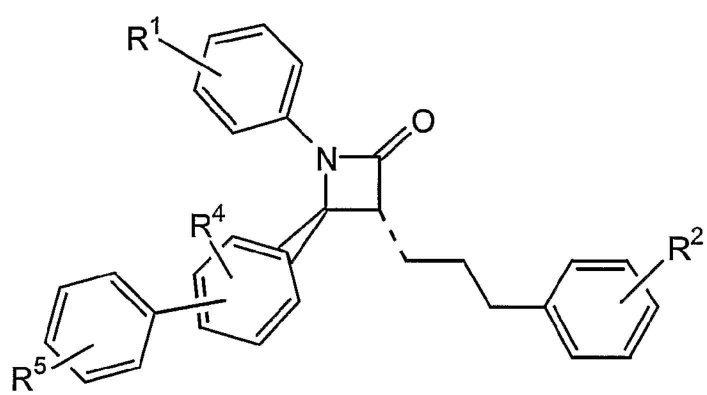
[0081] Throughout this application, various references are referred to. Each of the patents, patent applications, patent publications, and references mentioned herein is hereby incorporated by reference in its entirety.

[0082] The term "mammal" is used in its dictionary sense. The term "mammal" includes, for example, mice, hamsters, rats, cows, sheep, pigs, goats, and horses, monkeys, dogs (e.g., Canis familiaris), cats, rabbits, guinea pigs, and primates, including humans.

[0083] The compounds described herein contain two or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. Each chiral center may be defined, in terms of absolute stereochemistry, as ®- or (S)-.

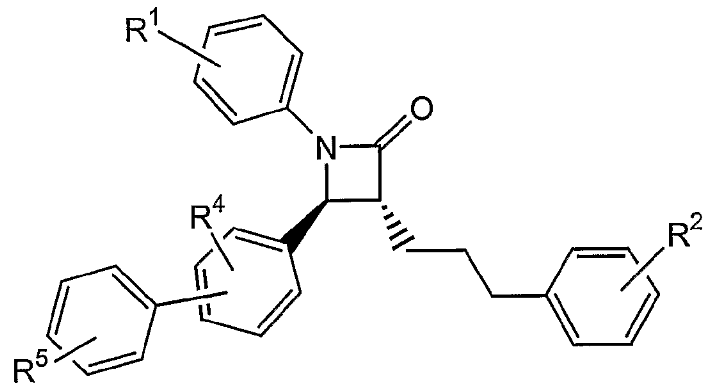
The present invention is meant to include all such possible isomers, as well as, their racemic and optically pure forms. Optically active ®- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

[0084] The graphic representations of racemic, ambiscalemic and scalemic or enantiomerically pure compounds used herein are taken from Maehr J. Chem. Ed. 62, 114-120 (1985): solid and broken wedges are used to denote the absolute configuration of a chiral element; wavy lines and single thin lines indicate disavowal of any stereochemical implication which the bond it represents could generate; solid and broken bold lines are geometric descriptors indicating the relative configuration shown but denoting racemic character; and wedge outlines and dotted or broken lines denote enantiomerically pure compounds of indeterminate absolute configuration. Thus, the formula XI is intended to encompass both of the pure enantiomers of that pair:

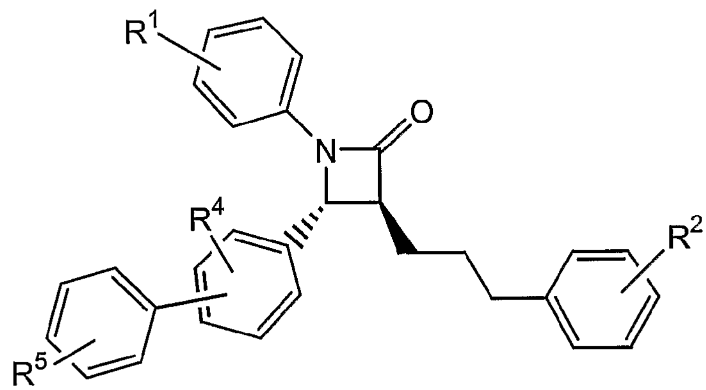


XI

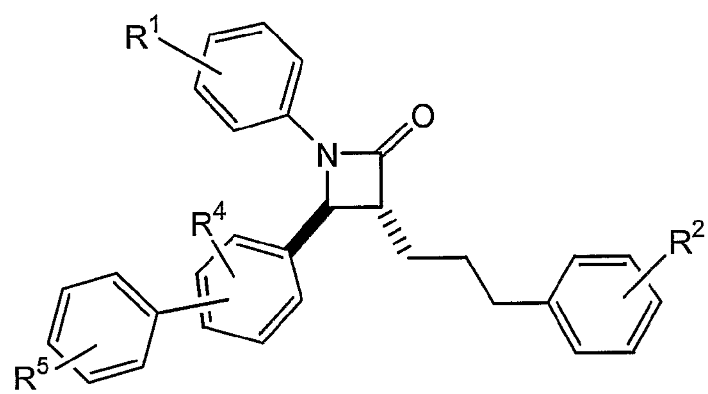
[0085] Means either pure R,S:



or pure S,R:



whereas



refers to a racemic mixture of R,S and S,R, i.e. having a trans relative configuration on the beta lactam ring.

[0086] The term "enantiomeric excess" is well known in the art and is defined for a resolution of ab into a + b as

$$ee_a = \left(\frac{conc.\ of\ a\ -\ conc.\ of\ b}{conc.\ of\ a\ +\ conc.\ of\ b}\right)\ x\ 100$$

[0087] The term "enantiomeric excess" is related to the older term "optical purity" in that both are measures of the same phenomenon. The value of ee will be a number from 0 to 100, zero being racemic and 100 being pure, single enantiomer. A compound which in the past might have been called 98% optically pure is now more precisely described as 96% ee; in other words, a 90% ee reflects the presence of 95% of one enantiomer and 5% of the other in the material in question.

[0088] The configuration of any carbon-carbon double bond appearing herein is selected for convenience only and is not intended to designate a particular configuration; thus a carbon-carbon double bond depicted arbitrarily herein as E may be Z, E, or a mixture of the two in any proportion.

[0089] Terminology related to "protecting", "deprotecting" and "protected" functionalities occurs throughout this application. Such terminology is well understood by persons of skill in the art and is used in the context of processes which involve sequential treatment with a series of reagents. In that context, a protecting group refers to a group which is used to mask a functionality during a process step in which it would otherwise react, but in which reaction is undesirable. The protecting group prevents reaction at that step, but may be subsequently removed to expose the original functionality. The removal or "deprotection" occurs after the completion of the reaction or reactions in which the functionality would interfere. Thus, when a sequence of reagents is specified, as it is in the processes of the invention, the person of ordinary skill can readily envision those groups that would be suitable as "protecting groups". Suitable groups for that purpose are discussed in standard textbooks in the field of chemistry, such as Protective Groups in Organic Synthesis by T.W.Greene [John Wiley & Sons, New York, 1991], which is incorporated herein by reference. Particular attention is drawn to the chapters entitled "Protection for the Hydroxyl Group, Including 1,2- and 1,3-Diols" (pages 10-86).

[0090] The abbreviations Me, Et, Ph, Tf, Ts and Ms represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, toluenesulfonyl and methanesulfonyl respectively. A comprehensive list of abbreviations utilized by organic chemists (i.e. persons of ordinary skill in the art) appears in the first issue of each volume of the Journal of

Organic Chemistry. The list, which is typically presented in a table entitled "Standard List of Abbreviations" is incorporated herein by reference.

[0091] While it may be possible for the compounds of formulae Φ, Ψ and I - VIII to be administered as the raw chemical, it is preferable to present them as a pharmaceutical composition. According to a further aspect, the present invention provides a pharmaceutical composition comprising a compound of formula Φ, Ψ or I - VIII or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0092] The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), rectal and topical (including dermal, buccal, sublingual and intraocular) administration. The most suitable route may depend upon the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a compound of formula Φ, Ψ and I - VIII or a pharmaceutically acceptable salt or solvate thereof ("active ingredient") with the carrier, which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

[0093] Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

[0094] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or

granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide sustained, delayed or controlled release of the active ingredient therein. The pharmaceutical compositions may include a "pharmaceutically acceptable inert carrier", and this expression is intended to include one or more inert excipients, which include starches, polyols, granulating agents, microcrystalline cellulose, diluents, lubricants, binders, disintegrating agents, and the like. If desired, tablet dosages of the disclosed compositions may be coated by standard aqueous or nonaqueous techniques, "Pharmaceutically acceptable carrier" also encompasses controlled release means.

[0095] Compositions of the present invention may also optionally include other therapeutic ingredients, anti-caking agents, preservatives, sweetening agents, colorants, flavors (e.g. cinnamon), desiccants, plasticizers, dyes, and the like. Any such optional ingredient must be compatible with the compound of the invention to insure the stability of the formulation. The composition may contain other additives as needed, including for example lactose, glucose, fructose, galactose, trehalose, sucrose, maltose, raffinose, maltitol, melezitose, stachyose, lactitol, palatinite, starch, xylitol, mannitol, myoinositol, and the like, and hydrates thereof, and amino acids, for example alanine, glycine and betaine, and peptides and proteins, for example albumen.

[0096] Examples of excipients for use as the pharmaceutically acceptable carriers and the pharmaceutically acceptable inert carriers and the aforementioned additional ingredients include, but are not limited to binders, fillers, disintegrants, lubricants, anti-microbial agents, and coating agents such as:

[0097] BINDERS: polyethylene oxide, corn starch, citric acid monohydrate, potato starch, other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, methyl cellulose, pre-gelatinized starch (*e.g.*,

STARCH 1500® and STARCH 1500 LM®, sold by Colorcon, Ltd.), hydroxypropyl methyl cellulose, methyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, microcrystalline cellulose (*e.g.* AVICEL™, such as, AVICEL-PH-101™, -103™ and -105™, sold by FMC Corporation, Marcus Hook, PA, USA), or mixtures thereof;

[0098] FILLERS: talc, sodium choloride, aluminum oxide, iron oxides (e.g. yellow, black, red), red ferric oxide, yellow ferric oxide, magnesium carbonate, magnesium hydroxide, magnesium aluminate, aluminum magnesium hydroxide, calcium carbonate (*e.g.*, granules or powder), calcium dihydroxide, dibasic calcium phosphate, dibasic calcium phosphate anhydrous, triacetin, lactose, hydrous lactose, tribasic calcium phosphate, calcium sulfate (*e.g.*, granules or powder), microcrystalline cellulose, silicified microcrystalline cellulose, soybean lecithin, xanthar gum, silicic anhyride, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, or mixtures thereof;

[0099] DISINTEGRANTS: agar-agar, alginic acid, calcium carbonate, simethicone emulsion, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, crospovidone, povidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, clays, other algins, other celluloses, gums, or mixtures thereof;

[00100] SURFACTANTS: Tween 80 or polyoxyethylene-polyoxypropylene copolymer, polyoxyethylene sorbitan, or mixtures thereof;

[00101] LUBRICANTS: calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, palmitic acid, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil and soybean oil), zinc stearate, ethyl oleate, ethyl laurate, agar, syloid silica gel (AEROSIL 200, W.R. Grace Co., Baltimore, MD USA), a coagulated aerosol of synthetic silica (Degussa Co., Plano, TX USA), a pyrogenic silicon dioxide (CAB-O-SIL, Cabot Co., Boston, MA USA), or mixtures thereof;

[00102] ANTI-CAKING AGENTS: calcium silicate, magnesium silicate, silicon dioxide, colloidal silicon dioxide, talc, or mixtures thereof;

[00103] ANTIMICROBIAL AGENTS: benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, butyl paraben, cetylpyridinium chloride, cresol, chlorobutanol, dehydroacetic acid, ethylparaben, methylparaben, phenol, phenylethyl alcohol, phenylmercuric acetate, phenylmercuric nitrate, potassium sorbate, propylparaben, sodium benzoate, sodium dehydroacetate, sodium propionate, polysorbate, sorbic acid, thimersol, thymo, or mixtures thereof;

[00104] COATING AGENTS: sodium carboxymethyl cellulose, cellulose acetate phthalate, ethylcellulose, gelatin, pharmaceutical glaze, hydroxypropyl cellulose, hydroxypropyl methylcellulose (hypromellose), hydroxypropyl methyl cellulose phthalate, methylcellulose, polyethylene glycol (e.g. polyethylene glycol 8000, polyethylene glycol 3000), polyvinyl acetate phthalate, shellac, sucrose, titanium dioxide, carnuba wax, candellilla wax, microcrystalline wax, or mixtures thereof;

[00105] COLORANTS: FD&C blue no.1, D&C yellow #10 aluminum lake, FD&C yellow #6/sunset yellow FCF aluminum lake, FD&C carmine aluminum lake and FD&C blue #1, or mixtures thereof; and

[00106] ANTIOXIDANTS: butylated hydroxyanisole, sodium ascorbate, sodium metabisulfate, malic acid, citric acid, ascorbic acid, butylated hydroxytoluene, vitamin C, propyl gallate, or mixtures thereof.

[00107] Solid oral dosage forms may optionally be treated with coating systems (e.g. Opadry® fx film coating system, for example Opadry® blue (OY-LS-20921), Opadry® white (YS-2-7063), Opadry® white (YS-1-7040), and black ink (S-1-8106).

[00108] The dose range for adult humans is generally from 0.005 mg to 10 g/day orally. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the invention which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 200 mg. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors, including the age and sex of the patient, the precise disorder being treated, and its severity.

[00109] A dosage unit (e.g. an oral dosage unit) can include from, for example, 1 to 30 mg, 1 to 40 mg, 1 to 100 mg, 1 to 300 mg, 1 to 500 mg, 2 to 500 mg, 3 to 100 mg,

5 to 20 mg, 5 to 100 mg (e.g. 1 mg, 2 mg, 3 mg, 4mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg) of a compound described herein.

Combination Therapy

[00110] Combination therapy can be achieved by administering two or more agents, each of which is formulated and administered separately, or by administering two or more agents in a single formulation. Other combinations are also encompassed by combination therapy. For example, two agents can be formulated together and administered in conjunction with a separate formulation containing a third agent. While the two or more agents in the combination therapy can be administered simultaneously, they need not be. For example, administration of a first agent (or combination of agents) can precede administration of a second agent (or combination of agents) by minutes, hours, days, or weeks. Thus, the two or more agents can be administered within minutes of each other or within 1, 2, 3, 6, 9, 12, 15, 18, or 24 hours of each other or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 days of each other or within 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks of each other. In some cases even longer intervals are possible. While in many cases it is desirable that the two or more agents used in a combination therapy be present in within the patient's body at the same time, this need not be so. Combination therapy can also include two or more administrations of one or more of the agents used in the combination. For example, if agent X and agent Y are used in a combination, one could administer them sequentially in any combination one or more times, e.g., in the order X-Y-X, X-X-Y, Y-X-Y, Y-Y-X, X-X-Y-Y, etc. Combination therapy can also include the administration of two or more agents via different routes or locations. For example, (a) one agents is administered orally and another agents is administered intravenously or (b) one agent is administered orally and another is administered locally into the site of injury (e.g., an artery). In each case, the agents can either simultaneously or sequentially. Approximated dosages for some of the combination therapy agents

described herein are found in the "BNF Recommended Dose" column of tables on pages 11-17 of WO01/76632 (the data in the tables being attributed to the March 2000 British National Formulary) and can also be found in other standard formularies and other drug prescribing directories. For some drugs, the customary presecribed dose for an indication will vary somewhat from country to country.

Dyslipidemic agents

[00111] The compounds described herein can be used in therapeutic combination with one or more dyslipidemic agents. Suitable dyslipidemic agents for use in therapeutic combination with a compound described herein include bile acid sequestrants such as cholestyramine (a styrene-divinylbenzene copolymer containing quaternary ammonium cationic groups capable of binding bile acids, such as Questran® or Questran Light® cholestyramine which are available from Bristol-Myers Squibb), colesevelam hydrochloride (such as WelChol® Tablets (polyallylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide) which are available from Sankyo), colestipol (a copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane, such as Colestid® tablets which are available from Pharmacia), dialkylaminoalkyl derivatives of a cross-linked dextran, LoCholest®, DEAE-Sephadex (Secholex®, Polidexide®), water soluble derivatives such as 3,3-ioene, N-(cycloalkyl)alkylamines and poliglusam, insoluble quaternized polystyrenes, saponins and mixtures thereof and those bile acid sequestrants disclosed in WO97/11345, WO98/57652, US3692895, and US5703188. Suitable inorganic cholesterol sequestrants include bismuth salicylate plus montmorillonite clay, aluminum hydroxide and calcium carbonate antacids.

[00112] HMG-CoA reductase inhibitors are dyslipidemic agents that can be used in therapeutic combinations with compounds described herein. Suitable HMG-CoA reductase inhibitors for use in therapeutic combination with a compounds described herein include: atorvastatin (Lipitor®; disclosed in US4681893, US5385929 and US5686104), atorvastatin calcium (disclosed in US5273995), dihydrocompactin, (disclosed in US4450171), bervastatin (disclosed in US5082859), carvastatin,

cerivastatin (Baycol®; disclosed in US5006530, US5502199, and US5177080), crilvastatin, dalvastatin/ RG 12561 (disclosed in EP738510A2), fluvastatin (Lescol®; disclosed in US4739073 and US534772), glenvastatin, fluindostatin/ XU 62-320 (disclosed in EP363934A1), velostatin (visinolin; disclosed in US4448784 and US4450171), lovastatin (mevinolin; MK-803; Mevacor® (Merck and Co.) and related compounds disclosed in US4231938), Advicor/ Nicostatin (a lovastatin-niacin mixture), mevastatin (and related compound disclosed in US3983140), compactin/ ML 236B/ CS 500/ 6-demethylmevinolin (and related compounds disclosed in US4804770), pitavastatin (also known as NK-104, itavastatin, nisvastatin, nisbastatin disclosed in US5102888), pravastatin (Eptastatin; CS-514; Pravachol® (Bristol Myers Squibb) and related compounds disclosed in US4346227), rivastatin (sodium 7-(4-fluorophenyl)-2,6-diisopropyl-5-methoxymethylpyridin-3-yl)-3,5-dihydroxy-6-heptanoate), rosuvastatin/rosuvastatin calcium (Crestor®; also known as ZD-4522 or atavastatin or visastatin; disclosed in US5260440), simvastatin (MMK-733; Zocor® (Merck and Co.) and related compounds as disclosed in US4448784 and US4450171), sirrivastatin, CI-981, PD134967-15, PD 135022, BMY-22089, PD 135023-15, BMY21950, PD 134965, dihydroxy open statins as disclosed in US2005010561, compounds disclosed in WO03/033481, US20050085497, US4231938, US4444784, US4647576, US4686237, US4499289, US4346227, US5753675, US4613610, EP0221025, and EP491226, and optical or geometric isomers thereof; and nontoxic pharmaceutically acceptable salts, N-oxides, esters, quaternary ammonium salts, and prodrugs thereof. In HMG-CoA reductase inhibitors where an open-acid form can exist, salt and ester forms may preferably be formed from the open-acid, and all such forms are included within the meaning of the term "HMG-CoA reductase inhibitor" as used herein. Pharmaceutically acceptable salts with respect to the HMG-CoA reductase inhibitor includes non-toxic salts of the compounds which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium, as well as those salts formed from amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine,

diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenzim- idazole, diethylamine, piperazine, and tris(hydroxymethyl) aminomethane. Further examples of salt forms of HMG-CoA reductase inhibitors may include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate.

[00113] Prodrugs of HMG CoA reductase inhibitors are also dyslipidemic agents. In certain embodiments, the prodrug is a lipophilic ester comprising an ester prodrug linkage to the HMG-like moiety of the statin drug and a lipophilic group described, for example, in WO05023305. Lipophilic alcohols available which may be used to form such statin prodrugs, include, but are not limited to, methanol, ethanol, propan-1-ol, propan-2-ol, butan-1-ol, butan-2-ol, pentan-1-ol, hexan-1-ol, heptan-1-ol, octan-1-ol, nonan-1-ol, decan-1-ol, 2-ethyl-hexan-1-ol, 3,3, 5-trimethyl-cyclohexanol, 2-ethoxy- ethanol, and menthol. Examples of such lipophilic ester statin prodrugs include but are not limited to (3R, 5R)-3, 5- Dihydroxy-7- (2-isopropyl-4, 5-diphenyl-3-phenylcarbamoyl-pyrrol-1-yl)-heptanoic acid, (E)-(3R, 5S)-3, 5-Dihydroxy-7-(1-isopropyl-3-phenyl-lH-indol-2-yl)-hept-6-enoic acid, (E)- (3R, 5S)-3, 5-Dihydroxy-7-[4-isopropyl-2- (methanesulfonyl-methyl-amino)-6-phenyl- pyrimidin-5-yl] -hept-6-enoic acid, (E)- (3R, 5S)-7- (2-Cyclopropyl-4-phenyl-quinolin-3-yl)- 3,5-dihydroxy-hept-6-enoic acid, (E)- (3R, 5S)-7- (2, 6-Diisopropyl-5-methoxymethyl-4-phenyl-pyridin-3-yl) -3, 5-dihydroxy-hept-6-enoic acid, including free acid and pharmaceutically acceptable salt forms thereof. Hydroxylated statin forms and ester prodrugs thereof as described, for example, in WO05023305 are also dyslipidemic agents. Hydroxylated statins include but are not limited to (3R, 5R)-3-, 5-Dihydroxy-7- [2- (4-hydroxy-phenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1- yl] -

heptanoic acid, (E)- (3R, 5S)-3, 5-Dihydroxy-7- [3- (4-hydroxy-phenyl)-l-isopropyl-IH- indol-2-yl] -hept-6-enoic acid, (E)- (3R, 5S)-3, 5-Dihydroxy-7- [4- (4-hydroxy-phenyl)-6- isopropyl-2- (methanesulfonyl-methyl-amino)-pyrimidin-5-yl]-hept-6-enoic acid, (E)- (3R, 5S)-7- [2-Cyclopropyl-4- (4-hydroxy-phenyl)-quinolin-3-yl]-3, 5-dihydroxy-hept-6- enoic acid, (E)- (3R, 5S)-3, 5-Dihydroxy-7- [4- (4-hydroxy-phenyl)-2, 6-diisopropyl-5- methoxymethyl-pyridin-3-yl]-hept-6-enoic acid, including free acid and pharmaceutically acceptable salt forms thereof. Ester prodrugs of hydroxylated statins are of the general formul X-Y, where is X is a hydroxylated statin (e.g., (3R, 5R)-3-, 5-Dihydroxy-7- [2- (4-hydroxy-phenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-heptanoic acid, (E)- (3R, 5S)-3, 5-Dihydroxy-7- [3- (4-hydroxy-phenyl)-l-isopropyl-lH-indol-2-yl]-hept-6-enoic acid, (E)- (3R, 5S)-3, 5-Dihydroxy-7- [4- (4-hydroxy-phenyl)-6-isopropyl-2- (methanesulfonyl-methyl-amino)- pyrimidin-5-yl] -hept-6-enoic acid, (E)- (3R, 5S)-7- [2-Cyclopropyl-4- (4-hydroxy-phenyl)-quinolin-3-yl] -3,5-dihydroxy-hept-6-enoic acid and (E)- (3R, 5S)-3, 5-Dihydroxy-7- [4- (4- hydroxy-phenyl) -2,6-diisopropyl-5-methoxymethyl-pyridin-3-yl]-hept-6-enoic acid) and Y is chosen from formic acid, acetic acid, propan-1-oic acid, propan- 2-oic acid, butan-1-oic acid, butan-2-oic acid, pentan-1-oic acid, hexan-1-oic acid, heptan- 1-oic acid, octan-1-oic acid, nonan-1-oic acid, decan-1-oic acid, benzoic acid, cinnamic acid and 1-hydroxy-benzoic acid. Not limiting examples of ester prodrugs of hydroxylated statins are shown in WO05023305, figure 10.

[00114] Lipid modulating agents are dyslipidemic agents which function as high density lipoprotein (HDL), including synthetic HDL which contains lipid such as phosphotidyl choline, phosphatidyl serine, phosphatidyl ethanolamine, and other phospholipids in combination with HDL associated proteins such as ApoA-I or variants thereof including ApoAI-Milano (R173C) and biologically active peptides derived therefrom, the ApoA-I Paris variant (R151C), the reverse lipid transport (RLT) peptides, enzymes associated with HDL such as paraoxonase, and apo E, alone or formulated in combination with liposomes or emulsions (an example of a liposomal formulation is found in WO95/23592), see, for example, US20030109442 and US20050096307. HDL associated proteins include sequences present in HDL associated proteins that associate with HDL and synthetic peptides having equivalent

binding or functional characteristics. HDL-associated proteins further include apolipoproteins such as Apo E, proApoA-I, ApoA-IParis, ApoA-II, proApoA-II, ApoA-IV, ApoC-I, ApoC-II, ApoC-III, including variants thereof which have been modified to include one or more sulfhydral groups, as described by Bielicki and Oda, Biochemistry 41:2089-2096 (2002). HDL-associated proteins further include paraoxonase, cholesteryl ester transfer protein, Lecithin Cholesterol Acyltransferase (LCAT), phospholipid transfer protein, including combinations thereof complexed with and without lipid. HDL-associated proteins can be used alone, in combination, complexed to one or more lipids alone or in combination complexed to one or more lipids. Non limiting examples include complexes comprising ApoA-I and lipid, complexes comprising paraoxanase and lipid, and complexes comprising ApoA-I, paraoxonase and lipid. HDL-associated proteins and lipids can be mixed in an aqueous solution in appropriate ratios complexed by methods known in the art and including freeze-drying, detergent solubilization followed by dialysis, microfluidization, sonication, and homogenization. Complex efficiency can be optimized, for example, by varying pressure, ultrasonic frequency, or detergent concentration. An example of a detergent commonly used to prepared HDL-associated protein-lipid complexes is sodium cholate. In some cases it is desirable to mix the lipid and the HDL-associated protein prior to administration. Lipids may be in solution or in the form of liposomes or emulsions formed using standard techniques such as sonication or extrusion. Sonication is generally performed with a tip sonifier, such as a Branson tip sonifier, in an ice bath. Typically, the suspension is subjected to several sonication cycles. Extrusion may be carried out by biomembrane extruders, such as the Lipex Biomembrane Extruder. Defined pore size in the extrusion filters may generate unilamellar liposomal vesicles of specific sizes. The liposomes may also be formed by extrusion through an asymmetric ceramic filter, such as a Ceraflow Microfilter, commercially available from the Norton Company, Worcester Mass. or through a polycarbonate filter or other types of polymerized materials (i.e. plastics) commonly known. In some cases, the dyslipidemic agent comprises an HDL-associated protein with little or no lipid. Non limiting examples of lipids include phospholipids (such as soy phosphatidylcholine, egg phosphatidylcholine, soy

phosphatidylglycerol, egg phosphatidylglycerol, palmitoyl-oleoyl-phosphatidylcholine distearoylphosphatidylcholine, distearoylphosphatidylglycerol, phosphatidylcholine, phosphatidylglycerol, sphingomyelin, phosphatidylserine, phosphatidic acid, N-(2,3-di(9-(Z)-octadecenyloxy))-prop-1-yl-N,N,N-trimethylammonium chloride, phosphatidylethanolamine, lysolecithin, lysophosphatidylethanolamine, phosphatidylinositol, cephalin, cardiolipin, cerebrosides, dicetylphosphate, dioleoylphosphatidylcholine, dipalmitoylphosphatidylcholine, dipalmitoylphosphatidylglycerol, dioleoylphosphatidylglycerol, stearoyl- palmitoyl-phosphatidylcholine, di-palmitoyl-phosphatidylethanolamine, distearoyl-phosphatidylethanolamine, dimyrstoyl-phosphatidylserine, and dioleyl-phosphatidylcholine) and non-phosphorus containing lipids (such as stearylamine, docecylamine, acetyl palmitate, and fatty acid amides). Additional lipids suitable for use are well known to persons of skill in the art and are cited in a variety of well known sources, e.g., McCutcheon's Detergents and Emulsifiers and McCutcheon's Functional Materials, Allured Publishing Co., Ridgewood, N.J. Generally, it is desirable that the lipids are liquid-crystalline at 37°C, 35°C, or 32°C. The concentration of the lipid in the formulation may vary. Persons of skill may vary these concentrations to optimize treatment with different lipid components or of particular patients. ApoAl is combined with lipid in a ratio by weight of between 1:0.5 to 1:3. In certain embodiments, more lipid being preferred for clearance of cholesterol. The ratio may be around 1:1 is to produce the most homogenous population and for purposes of producing stable and reproducible batches. In certain embodiments, the lipid modulating agent is ETC-216, which is a synthetic HDL complex composed of 14 mg/mL of recombinant apolipoprotein A-I Milano and 13 mg/mL of 1-palmitoyl-2-oleoyl phosphatidyl choline (POPC) complex in sucrose-mannitol-phosphate buffer solution (sterile 6.4% sucrose, 0.8% mannitol in 6 mmol/L phosphate buffer, pH 7.4) (Esperion Therapeutics, Inc.), as a ready to inject solution or saline.

[00115] Other dyslipidemic agents which can be used a therapeutic combination with a compound described herein include:

cysteinyl leukotriene 2 receptor (CysLT2) antagonists some of which are also antagonists of the cysteinyl leukotriene 1 receptor (CysLT1) such as 3- (

(carboxyacetal) amino) phenyl) thio)-4-nonyl-oxobenzenehexanoic acid, methylbutanoic acid, and those described in WO05/082346;

peptides and peptide analogues that mimic the structural and pharmacological properties of human ApoA-I including those disclosed, for example in US6004925;

apolipoprotein E (apoE) and isoforms thereof including that produced by the methods disclosed in WO04/108922 and US5834596;

apolipoprotein A (apoA) and isoforms thereof including that produced by the methods disclosed in WO04/108922;

ApoA-I agonists including the peptides described in US6004925 and US6037323;

HMG-CoA synthase inhibitors such as L-659,699 ((E,E)-11-[3'R-(hydroxy-methyl)-4'-oxo-2'R-oxetanyl]-3,5,7R-trimethyl-2,4-undecadienoic acid) and those disclosed in US5120729, US5064856, and US4847271;

cholesterol absorption inhibitors such as plant sterols, plant stanols and/or fatty acid estesrs of plant stanols such as sitostanol ester used in Benecol® margarine, stanol esters, beta-sitosterol, sterol glycosides such as tiqueside, pamaqueside, (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one (Zetia®), and the compounds disclosed in USRE37721, WO9302048, WO05044256, WO05033100, WO05021495, WO05021497, WO05009955, WO05000353, WO04087655, WO04000804, WO04000803, WO02050068, WO02050060, WO02050027, WO04000805, WO02066464, WO03026672, WO05042692, WO05042692, and WO04005247;

phytoestrogen compounds such as disclosed in WO00/30665 including isolated soy bean protein, soy protein concentrate or soy flour as well as an isoflavone such as genistein, daidzein, glycitein or equol, or phytosterols, phytostanol or tocotrienol as disclosed in WO00/015201;

an α-glucosidase inhibitor, an aldose reductase inhibitor and/or an LDL catabolism promoter such as disclosed in EP1022272;

a matrix metalloproteinase inhibitor including but not limited to (±)4-(4'-Chloro-biphenyl-4-yl)-4-hydroxy-butyric acid, (L)-2-(Dibenzofuran-2-sulfonylamino)-3-mercapto-propionic acid, (L)-2-(Dibenzofuran-2-sulfonylamino)-3-methyl-butyric acid, (L)-2-(Dibenzofuran-2-sulfonylamino)-3-phenyl-propionic acid, (L)-2-

(Dibenzofuran-2-sulfonylamino)-3-tritylsulfanyl-propionic acid, (L)-2-(Dibenzofuran-2-sulfonylamino)-4-methyl-pentanoic acid, (S)-2-(4'-Amino-biphenyl-4-sulfonylamino)-3-methyl-butyric acid, (S)-2-(4'-Bromo-biphenyl-4-sulfonylamino)-3-methyl-butyric acid, (S)-2-(4'-Bromo-biphenyl-4-sulfonylamino)-3-phenyl-propionic acid, (S)-2-(Dibenzofuran-2-sulfonylamino)-4-phenyl-butyric acid, (S)-2-(dibenzofuran-3-sulfonylamino)-3-methyl-butyric acid, (S)-2-(dibenzofuran-3-sulfonylamino)-succinic acid, (S)-2-[4-(4-Benzyl-piperidin-1-yl)-benzenesulfonyl-amino]-3-phenyl-propionic acid, (S)-2-{4-[-4-(4-Methoxy-phenyl)-piperazin-1-yl]-benzenesulfonylamino}-phenyl-propionic acid, (S)-2-Acetylamino-4-dibenzofuran-2-yl-4-oxo-butyric acid, (S)-2-Amino-4-dibenzofuran-2-yl--4-oxo-butyric acid, (S)-3-Methyl-2-(4'-nitro-biphenyl-4-sulfonylamino)-butyric acid, (S)-3-Phenyl-2-[4-(4-phenyl-piperidin-1-yl)-benzene-sulfonylamino]-propionic acid, (S)-4-Dibenzofuran-2-yl-4-oxo-2-(2,2,2-trifluoroacetylamino)-butyric acid, (S)-4-Dibenzofuran-2-yl-4-oxo-2-(3-phenyl-propionylamino)-butyric acid, (S)-4-Dibenzofuran-2-yl-4-oxo-2-phenylacetylamino-butyricacid, [4-(4-Phenyl-piperidin-1-yl)--benzenesulfonylamino]-acetic acid, 2-(4'-bromobiphenyl-4-sulfonylamino)-3-methylbutyric acid, 2-(4'-Bromo-biphenyl-4-sulfonylamino)-3-methyl-butyric acid, 4-(4'-Bromo-biphenyl-4-yl)-4-hydroxyimino-butyric acid, 4-(4'-Chloro-biphenyl-4-yl)-4-(dimethylhydrazono)-butyric acid, 4-(4'-Chloro-biphenyl-4-yl)-4-hydroxyimino-butyric acid, 4-Oxo-4-[4-(4-phenyl-piperazin-1-yl)-phenyl]-butyric acid, 4-Oxo-4-[4-(4-phenyl-piperidin-1-yl)-phenyl]-butyric acid, batimastat, CDP-845 (Celltech), CGS27023A (Ciba-Giegy), CI-1026, fenbufen and related compounds disclosed in US3784701 and by Child et al., J Pharm Sci 1977; 66:466-476, galardin, marimastat, N-Hydroxy-2-[4-(4-phenyl-piperidin-1-yl)-benzene-sulfonylamino]-acetamide, N-Hydroxy-4-oxo-4-[4-(4-phenyl-piperidi-n-1-yl)-phenyl]-butyramide, PD 166793, RO-31-9790 (Roche), U24522 (Merck), and the compounds and/or peptides disclosed in EP0236872, EP0274453, EP0489577, EP0489579, EP0497192, EP0574758, EP2321081, US4599361, US5183900, US5256657, US5270326, US5300501, US5304604, US5455258, US552419, US5525629, US5530128, US5530161, WO90/05716, WO90/05719, WO91/02716, WO92/09563, WO92/13831, WO92/17460, WO92/22523, WO93/09090, WO93/09097, WO93/20047, WO93/244, WO93/24449, WO94/02446,

WO94/02447, WO95/13289, WO96/11209, WO97/27174, and US20050020607 (including the compounds specifically disclosed by chemical formula and name);
a sodium-proton exchange inhibitor such as disclosed in DE19622222;
an LDL-receptor inducer or a steroidal glycoside such as disclosed in US5698527 and GB2304106;
LUV (large unilamellar vesicles) products including ETC-588 (Pfizer);
acyl coenzyme A-cholesterol acyl transferase (ACAT) inhibitors such as avasimibe (Current Opinion in Investigational Drugs. 3(9):291-297 (2003)), eflucimibe, HL-004, lecimibe, (DuP-1), KY505, SMP 797, TS-962 (Taisho Pharmaceutical Co. Ltd), F-1394, CS-505 (pactimibe), F-12511, K-10085 and YIC-C8-434, CL-277,082 (Clin Pharmacol Ther. 48(2):189-94 (1990)) and those disclosed in Drugs of the Future 24, 9-15 (1999); Nicolosi et al, Atherosclerosis (1998), 137(1), 77-85; Ghiselli and Giancarlo, Cardiovasc. Drug Rev. (1998), 16(1), 16-30; Smith, et al, Bioorg. Med. Chem. Lett. (1996), 6(1), 47-50; Krause et al, Inflammation: Mediators Pathways (1995), 173-98, Publisher: CRC, Boca Raton, Fla; Sliskovic et al, Curr. Med. Chem. (1994), 1(3), 204-25; Stout et al, Chemtracts: Org. Chem. (1995), 8(6), 359-62 and US5510379, WO96/26948 and WO96/10559;
CETP inhibitors such as JTT-705 (JTT 705, identified in Nature 406, (6792):203-7 (2000), torcetrapib (CP-529,414 described in US20030186952 and WO00/017164), CP 532,632, BAY63-2149, CeTi-1, SC 591, SC 795 (Pharmacia), SC 744 (Pharmacia) and the like including those described in Current Opinion in Investigational Drugs. 4(3):291-297 (2003) and those disclosed in J. Antibiot., 49(8): 815-816 (1996), Bioorg. Med. Chem. Lett., 6:1951-1954 (1996), J. Medicinal Chemisty 49(1): 1-22, and patent publications US5512548, US6147090, WO99/20302, WO99/14204, WO99/41237, WO95/04755, WO96/15141, WO96/05227, WO038721, WO/0038722, EP796846, EP818197, EP818448, EP992496, DE19704244, DE19741051, DE19741399, DE197042437, DE19709125, DE19627430, DE19832159, DE19741400, JP 11049743, and JP 09059155;
squalene synthetase inhibitors such as squalestatin-1, and those disclosed in US4871721, US4924024, US5712396 (α-phosphono-sulfonates), Biller et al (1988) J. Med. Chem., 31:1869 (e.g., isoprenoid (phosphinyl-methyl)phosphonates), Biller et al

(1996) Current Pharmaceutical Design, 2:1, P. Ortiz de Montellano et al (1977) J. Med. Chem. 20:243 (terpenoid pyrophosphates), Corey and Volante (1976) J. Am. Chem. Soc., 98:1291 (farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs), McClard et al (1987) J.A.C.S., 109:5544 (phosphinylphosphonates), Capson, T. L., PhD dissertation, June, 1987, Dept. Med. Chem. U of Utah, Abstract, Table of Contents, pp 16, 17, 40-43, 48-51, Summary, (cyclopropanes), Curr. Op. Ther. Patents (1993) 861, and patent publications EP0567026Al, EP0645378Al, EP0645377Al, EP0611749Al, EP0705607A2, EP0701725Al, US20040072830, and WO96/09827;

antioxidants such as probucol (and related compounds disclosed in US3674836), probucol derivatives such as AGI-1067 ([mono[4-[[1-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]thio]-1-methylethyl]thio]-2,6-bis(1,1-dimethylethyl)phenyl] ester] (butanedioc acid) and other derivatives disclosed in US6121319 and US6147250), tocopherol, ascorbic acid, retinol (as disclosed in WO94/15592), β-carotene, selenium, vitamin C and pharmaceutically acceptable salts and esters thereof;

an antihomocysteine agent such as folic acid, folate, vitamin E, vitamin B_6, vitamin B_{12} and pharmaceutically acceptable salts and esters thereof;

PPARα agonists such as those disclosed in US6028109 (fluorophenyl compounds), WO00/75103 (substituted phenylpropionic compounds), WO98/43081 and fibric acid derivatives (fibrates) such as beclofibrate, benzafibrate, bezafibrate (CAS RN 41859-67-0, see US3781328), binifibrate (CAS RN 69047-39-8, see BE884722), ciprofibrate (CAS RN 52214-84-3, see US3948973), clinofibrate (CAS RN 30299-08-2, see US3716583), clofibrate (such as ethyl 2-(p-chlorophenoxy)-2-methyl-propionate, e.g., Atromid-S® capsules (Wyeth-Ayerst), clofibric acid, etofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate, fenofibrate (such as Tricor® micronized fenofibrate ((2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester; Abbott Laboratories) or Lipanthyl® micronized fenofibrate (Labortoire Founier, France)), gemcabene, gemfibrozil (such as 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid, e.g., Lopid® tablets (Parke Davis)), lifibrol, GW 7647, BM 170744, LY518674 and those fibrate and fibrate acid derivatives disclosed in

WO03/033456, WO03/033481, WO03/043997, WO03/048116, WO03/053974, WO03/059864, and WO03/05875;

FXR receptor modulators such as GW 4064 (described in WO00/37077, Glaxo Group Limited), SR 103912, 3-deoxychenodeoxycholic acid, QRX-401 (QuatRx), (E)-and (Z)-guggulsterone, chenodeoxycholic acid (CDCA), 6alpha-ethyl-chenodeoxycholic acid (6-ECDCA), compounds disclosed in WO05056554 (including the compounds specifically named in claims 3, 7, 9, 11, 13, 17, 19, 21 23, 27, 29, 31, 33, 35, 37, 39, and 41), compounds disclosed in US6906057 (such as (Z)-5-[2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronapthalen-2-yl)-2-(trimethylsilyl)vinyl]thiophene-2-carboxylic acid, (Z)-5-[2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronapthalen-2-yl)-2-(trimethylsilyl)vinyl]thiophene-2-carboxylic acid and the compounds described in claims 26-28), farnesol (3,7,11,trimethyl-2,6,10-dodecatrienol), farnesal, farnesyl acetate, farnesoic acid, geranylgeraniol, and juvenile hormone III (7-methyl-9-(3,3-dimethyloxiranyl)-3-methyl-2,6-nonadienoic acid methyl ester), methyl farnesyl ether, ethyl farnesyl ether, methyl turnesoztce, ethyl Carnesoate, 7-methyl-9-(3,3-dimethyloxiranyl)-3-methyl-2,6-nonadienoic acid methyl ester, and 7-methyl-9-(3,3-dimethyloxiranyl)-3-methyl-2,6-nonadienoic acid ethyl ester, compounds disclosed in WO04/048349 (such as 3-{[(4-{[3-(2,6-Dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}-2-methylphenyl)- (methyl) amino] methyl} benzoic acid ; Methyl 4-0[(4-{[3-(2,6-dichlorophenyl)-5-isopropyl-4-isoxazolyl]methoxy}-2- dimethylanilino) methyl] benzoate ; 3-{[(2-Chloro-4-{[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}- phenyl) amino] methyl} benzoic acid ; 5-[(4-{[3-(2,6-Dichlorophenyl)-5-isopropyl-4-isoxazolyl]methoxy}-2-dimethyl- anilin) methyl]-2-furoic acid; 4- [(4-1 [3- (2, 6-Dichlorophenyl)-5-isopropyl-4-isoxazolyllmethoxy}-2-dimethyl- anilino) methyl] benzoic acid; Methyl 2-[(4-{[3-(2,6-dichlorophenyl)-5-isopropyl-4-isoxazolyl]methoxy}-2- dimethylanilino) methyl]-3-furoate ; N- (2, 1, 3-Benzoxadiazol-5-ylmethyl)-4- { [3- (2, 6-dichlorophenyl)-5-isopropyl-4-isoxazolyl]methoxy}-N,2-dimethylaniline ; N-(4-{[3-(2,6-Dichlorophenyl)-5-isopropyl-4-isoxazolyl]methoxy}-2-methylphenyl)- N-methyl-N-[4-(1, 2, 3-thiadiazol-4-yl) benzyl] amine ; 4- [(4-1 [3- (2, 6-Dichlorophenyl)-5-isopropyl-4-isoxazolyllmethoxy}-2-dimethyl- anilino)methyl]benzonitrile ; 2-[(4-{[3-(2,6-

Dichlorophenyl)-5-isopropyl-4-isoxazolyl]methoxy}-2-dimethyl- anilin) methyl]-3-furoic acid; {3- [(4- { [3-(2, 6-Dichlorophenyl)-5-isopropyl-4-isoxazolyl] methoxy} -2- dimethylanilino) methyl] phenyl} methanol ; {4- [(4- { [3-(2,6-Dichlorophenyl)-5-isopropyl-4-isoxazolyl]methoxy}-2- dimethylanilino)methyl]phenyl}methanol ; 3- [(4- { [3- (2, 6-Dichlorobenzyl)-5-ethyl-4-isoxazolyl] methoxy}-2- dimethylanilino) methyl] benzoic acid; 3-{[(4-{[5-Isopropyl-3-(2, 4, 6-trichlorophenyl)isoxazol-4-yl]methoxy}-2- methylphenyl)- (methyl) amino] methyl} benzoic acid ; 3- [(4-1 [3-(2, 6-Dichlorobenzyl)-5-isopropyl-4-isoxazolyi] methoxy} -2- dimethylanilino) methyl] benzoic acid ; 3-{[(4-{[3-(2-Chlorobenzyl)-5-isopropylisoxazol-4-yl]methoxy}-2-methylphenyl)- (methyl)-amino] methyl} benzoic acid ; 3-[(4-{[5-Cyclopropyl-3-(2,6-dichlorobenzyl)-4-isoxazolyl]methoxy}-2- dimethylanilino) methyl] benzoic acid ; 5-{[5-({5-Isopropyl-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl}methoxy)-2- dimethylanilino] methyl}-2-furoic acid ; 4-{ [4-({5-isopropyl-3- [2-(trifluoromethoxy) phenyl]-4-isoxazolyl} methoxy)-2- dimethytanitino] methyt} benzoicacid ; 3-{[4-({5-Isopropyl-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl}methoxy)-2- dimethylanilino] methyl} benzoic acid ; Methyl 5-{[4-({5-isopropyl-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl}methoxy)-2- dimethylanilino] methyl}-2-furoate ; Methyl 4- { [4- ({5-isopropyl-3- [2- (trifl uoromethoxy) phenyl]-4-isoxazolyl} methoxy)-2- dimethylanilino] methyl} benzoate ; 4-1 [(2-Chloro-4-1 [3- (2, 6-dichlorophenyl)-5-isopropylisoxazol-4-yllmethoxy} phenyl)- amino] carbonyl} benzoic acid; Methyl 3-[(2-chloro-4-{[3-(2,6-dichlorophenyl)-5-isopropyl-4-isoxazolyl]methoxy}- anilino) carbonyl] benzoate; Methyl 4-[(2-chloro-4-{[3-(2,6-dichlorophenyl)-5-isopropyl-4-isoxazolyl]methoxy}- anilino) carbonyl] benzoate ; 3- [(4- { [3- (2, 6-Dichlorophenyl)-5-isopropyl-4-isoxazolyl] methoxy}-2-methylanilino)-carbonyl] benzoic acid; 4-[(4-{[3-(2,6-Dichlorophenyl)-5-isopropyl-4-isoxazolyl]methoxy}-2-methylanilino)- carbonyl] benzoic acid; 3- [(2-Chloro-4-{[3-(2,6-dichlorophenyl)-5-isopropyl-4-isoxazolyl]methoxy}- anilin) carbonyl] benzoic acid ; 3-[(4-{ [3-(2, 6-Dichlorophenyl)-5-isopropyl-4-isoxazolyl] methoxy}-2-dimethylanilino) carbonyl] benzoic acid ; 3-[(2-Chloro-4-{[3-(2,6-dichlorophenyl)-5-isopropyl-4-isoxazolyl]methoxy}- methylanilino) carbonyl] benzoic acid ; 4-[(2-Chloro-4-{[3-(2,6-dichlorophenyl)-5-isorpopyl-4-isoxazolyl]methoxy}-

methylanilino) carbonyl] benzoic acid ; 3- { [4-({5-isopropyl-3-[2-(trifluoromethoxy) phenyl]-4-isoxazolyl} methoxy) -2- dimethylanilino] carbonyl} benzoic acid; 3- { [4-({5-lsopropyl-3-[2-(trifluoromethoxy) phenyl]-4-isoxazolyl} methoxy) -2- methylanilino] carbonyl} benzoic acid ; 3-{ [2-Chloro-4-({5-isopropyl-3-[2-(trifluoromethoxy) phenyl]-4-isoxazolyl}- methoxy) methylanilino] carbonyl} benzoic acid ; Methyl 3- { [(4-{[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}-2-methylphenyl) (methyl) amino] sulfonyl} benzoate; Methyl 3-{[(2-chloro-4- { [3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}- phenyl) amino] sulfonyl} benzoate; Methyl 3-{[(4-{[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}-2- methylphenyl)amino]sulfonyl} benzoate; Methyl 3-{[(4-{[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4 yl]methoxy}phenyl)- amino]- sulfonyl} benzoate; 3-{[(4-{[3-(2,6-Dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}-2-methylphenyl)- amino] sulfonyl} benzoic acid; 3- { [(4-{ [3-(2, 6-Dichlorophenyl)-5-isopropylisoxazol-4-yl] methoxy} phenyl) amino- sulfonyl} benzoic acid; Methyl 3-{[(2-chloro-4-{[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}- phenyl) (methyl) amino] sulfonyl} benzoate; Methyl 3-{[(4-{[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}phenyl)- (methyl) amino] sulfonyl} benzoate; Methyl 3-{[(2-chloro-4-{[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl] methoxy} -phenyl) (ethyl) amino] sulfonyl} benzoate ; Methyl 3- { [(4-{[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}-2-methyl- phenyl) (ethyl) amino]sulfonyl} benzoate; Methyl 3- { [(4- { [3-(2, 6-dichlorophenyl)-5-isopropylisoxazol-4-yl] methoxy} phenyl)- (ethyl)-amino] sulfonyl} benzoate ; 3- { [(2-Chloro-4- { [3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}phenyl)- amino] sulfonyl} benzoic acid; 3- { [(2-Chloro-4- { [3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}phenyl)- (methyl) amino] sulfonyl} benzoic acid; 3- { [(4- { [3- (2, 6-Dichlorophenyl)-5-isopropyl isoxazol-4-yl] methoxy}-2-methylphenyl)- (methyl) amino] sulfonyl} benzoic acid ; 3- { [(4-{[3-(2,6-Dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}phenyl)(methyl)- amino] sulfonyl} benzoic acid; 3- { [(2-Chloro-4-{[3-(2,6-dichlorophenyl)-5-isopropylisoazol-4-yl]methoxy}phenyl)-(ethyl) amino] benzoic acid; 3- { [(4- { [3- (2, 6-Dichlorophenyl)-5-isopropylisoxazol-4-yl] methoxy}-2-methylphenyl)- (ethyl) amino] sulfonyl} benzoic

acid ; 3- { [(4- { [3-(2, 6-Dichlorophenyl)-5-isopropylisoxazol-4-yl] methoxy} phenyl) (ethyl)- amino] benzoic acid; Methyl 4-{[(2-chloro-4-{[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}- phenyl)amino]sulfonyl}benzoate ; Methyl 4-{[(4- { [3-(2, 6-dichlorophenyl)-5-isopropylisoxazol-4-yl] methoxy}-2-methyl- phenyl) amino] sulfonyl} benzoate ; Methyl 4- { [(4-{[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}phenyl)- amino] benzoate ; 4-{[(2-Chloro-4-{[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}phenyl)-amino] sulfonyl} benzoic acid; 4-{[(4- { [3-(2, 6-Dichlorophenyl)-5-isopropyl isoxazol-4-yl] methoxy}-2-methylphenyl)- amino] suffonyl} benzoic acid; 4-{[(4-{[3-(2,6-Dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}phenyl)amino]- sulfonyl} benzoic acid; Methyl 4-{ [(4- { [3-(2, 6-dichlorophenyl)-5-isopropylisoxazol-4-yl] methoxy}-2-methyl- phenyl) (methyl) amino] benzoate ; Methyl 4- { [(4- { [3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}phenyl)- (methyl) amino]sulfonyl}benzoate ; Methyl 4- { [(4- { [3-(2, 6-dichlorophenyl)-5-isopropylisoxazol-4-yl] methoxy} phenyl)- (ethyl) amino] sulfonyl} benzoate ; 4-{[(2-Chloro-4-{[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}phenyl)-(methyl) aminolsulfonyllbenzoic acid; 4- { [(4-1 [3- (2, 6-Dichlorophenyl)-5-isopropylisoxazol-4-yl] methoxy}-2-methylphenyl)- (methyl) amino]sulfonyl}benzoic acid; 4-{[(4-{[3-(2,6-Dichlorophenyl)-5-isopropylisoxazol-4-yl] methoxy} phenyl) (methyl)- amino]sulfonyl}benzoic acid; 4-1 [(2-Chloro-4-1 [3- (2, 6-dichlorophenyl)-5-isopropylisoxazol-4-yi] methoxy} phenyl)- (ethyl) amino]sulfonyl}benzoic acid ; 4-{ [(4-{ [3-(2, 6-Dichlorophenyl)-5-isopropylisoxazol-4-yl] methoxy}-2-methyl phenyl)- (ethyl) amino]sulfonyl} benzoic acid ; 4- { [(4- { [3- (2, 6-Dichlorophenyl)-5-isopropylisoxazol-4- yl]methoxy}phenyl)(ethyl)amino]-sulfonyl} benzoic acid; 3-({[2-Chloro-4-({5-isopropyl-3-[2-(trifluoromethoxy)phenyl]isoxazol-4- yl} methoxy)-phenyl] amino} sulfonyl) benzoic acid ; 3-({[4-({5-isopropyl-3-[2-(trifluoromethoxy)phenyl]isoxazol-4-yl} methoxy) -2- methyl-phenyl]amino}sulfonyl)benzoic acid ; Methyl 3-{[[2-chloro-4-({5-isopropyl-3-[2-(trifluoromethoxy)phenyl]-isoxazol-4- yl} methoxy) phenyl (methyl) amino]sulfonyl} benzoate; Methyl 3- { [[4-({5-isopropyl-3-[2-(trifluoromethoxy)phenyl]isoxazol-4-yl} methoxy) - 2-methylphenyl](methyl)amino]sulfonyl} benzoate; 3- { [loro-4-({5-

isopropyl-3- [2-(trifluoromethoxy) phenyl] isoxazol-4- yl} methoxy)-phenyl] (methyl) amino] sulfonyl} benzoic acid ; 3-f [[4- ({5-Isopropyl-3- [2- (trifluoromethoxy) phenyl] isoxazol-4-yl} methoxy) -2- methyl-phenyl] (methyl) amino]sulfonyl}benzoic acid ; 3-1 [(4- { [3- (2, 6-Dichlorobenzyl)-5-ethylisoxazol-4-yllmethoxy}-2-methylphenyl)(methyl)-amino]sulfonyl}benzoic acid ; Methyl 4-[(2-chloro-4-{[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}- benzyl) oxy] benzoate ; Methyl 3-[(2-chloro-4-{[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl] methoxy} -benzyl)-oxy]benzoate ; 3-[(2-Chloro-4- { [3- (2, 6-dichlorophenyl)-5-isopropylisoxazol-4-yl] methoxy} - benzyl) oxy]-benzoic acid; 3- [loro-4- { [3-(2, 6-dichlorophenyl)-5-isopropylisoxazol-4-yl] methoxy}- benzyl) thio]-benzoic acid; 3-[(4-{[3-(2,6-Dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}-2-methylbenzyl)-oxy]-benzoic acid ; 3-[(4-{[3-(2,6-Dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}-2-methylbenzyl)- thio]-benzoic acid; 4- [(2-Chloro-4-1 [3- (2, 6-dichlorophenyl)-5-isopropylisoxazo1-4-yllmethoxy} benzyl)- oxy] benzoic acid ; 4-[(2-Chloro-4- { [3-(2, 6-dichlorophenyl)-5-isopropyl isoxazol-4-yl] meth oxy} benzyl)- thio]-benzoic acid ; Methyl 3-{[2-chloro-4-({5-isopropyl-3-[2-(trifluoromethoxy)-phenyl]isoxazol-4- yl methoxy) benzyl] oxy} benzoate ; Methyl 3-{[4-({5-isopropyl-3-[2-(trifluoromethoxy)phenyl]isoxazol-4-yl}methoxy)-2-methylbenzyl] oxy} benzoate ; 3- { [2-Chloro-4- ({5-isopropyl-3- [2- (trifl uoromethoxy) phenyl] isoxazol-4-yl} methoxy)- benzyl] oxy} benzoic acid; 3-{[4-({5-Isopropyl-3-[2-(trifluoromethoxy)phenyl]isoxazol-4-yl}methoxy)-2- methyl-benzyl] oxy} benzoic acid; 3- [(2-Chloro-4-{[3-(2,6-dichlorobenzyl)-5-ethylisoxazol-4-yl]methoxy}benzyl)oxy]- benzoic acid ; Methyl 3-{ [2-ch loro-4-({5-isopropyl-3-[2-(trifl uoro-methoxy) phenyl] isoxazol-4- yl}methoxy)benzyl]thio} benzoate; Methyl 3-{ [4-({5-isopropyl-3-[2-(trifluoromethoxy) phenyl] isoxazol-4-yl} methoxy) -2-methylbenzyl] thio} benzoate ; 3- { [2-Chloro-4- ({5-isopropyl-3- [2-(trifluoromethoxy) phenyl] isoxazol-4-yl} methoxy)- benzyl] thio} benzoic acid ; 3-{[4-({5-Isopropyl-3-[2-(trifluoromethoxy)-phenyl]isoxazol-4-yl} methoxy) -2-methyl-benzyl] thio} benzoic acid; Methyl 3-[(2-chloro-4-{[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4- yl]methoxy}benzyl)(methyl)amino]benzoate ; 3-[(2-Chloro-4-{[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}benzyl)- (methyl) amino]

benzoic acid; 3-[(2-Chloro-4-{[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}benzyl)- amino] benzoic acid ; Ethyl 3-{[2-chloro-4-({5-isopropyl-3-[2-trifluoromethoxy)phenyl]-4-isoxazolyl}- methoxy) benzyl] amino} benzoate ; 3- { [2-Chloro-4-({5-isopropyl-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl}methoxy)-benzyl] amino} benzoic acid; 3- [[2-Chloro-4- ({5-isopropyl-3- [2-(trifluoromethoxy) phenyl]-4-isoxazolyl} methoxy)- benzyl] (methyl) amino] benzoic acid; Methyl 4-[(4-{[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}-2-methylphenoxy) methyl] benzoate ; Methyl 3-[(2-chloro-4- { [3-(2, 6-dich lorophenyl)-5-isopropyl isoxazol-4-yl] methoxy} - phenoxy) methyl] benzoate ; Methyl 3-[(4-{[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}-2-methyl-phenoxy) methyl] benzoate; 3-[(2-Ch loro-4- { [3-(2, 6-dichlorophenyl)-5-isopropylisoxazol-4-yl] methoxy} phenoxy)- methyl] benzoic acid ; 3- [(4- { [3-(2, 6-Dichlorophenyl)-5-isopropylisoxazol-4-yl] methoxy}-2- methylphenoxy)-methyl] benzoic acid; and Methyl 4- [(4- { [3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy}-2-methyl- phenoxy) methyl]benzoate) and the like;

LXR receptor modulators such as α-hydroxycholesterol, 25-hydroxycholesterol, 27-hydroxy-cholesterol, 4β-hydroxycholesterol, 24-hydroxycholesterol, 20(S)-hydroxycholesterol, 22(R)-hydroxycholesterol, 20,22-dihydroxycholesterol, GW 3965, T9013137, and XTC0179628, and those disclosed in US20030125357, WO03/045382, WO03/053352, WO03/059874, and the like;

HM74 and HM74A (human HM74A is Genbank Accession No. AY148884 and rat HM74A is EMM_patAR098624) receptor agonists such as nicotinic acid (niacin) and derivatives thereof (e.g., compounds comprising a pyridine-3-carboxylate structure or a pyrazine-2-carboxylate structure, including acid forms, salts, esters, zwitterions and tautomers, where available) including but not limited to those disclosed in Wise et al (2003) J. Biol. Chem. 278: 9869 (e.g., 5-methylpyrazole-3-carboxylic acid and acifran (4,5-dihydro-5-methyl-4-oxo-5-phenyl-2-furan carboxylic acid pyradine-3-acetic acid)), as well as trans-metanicotine , epibatidine or one of its analogs, pyridol or derivatives thereof, piperidine alkaloids (such as lobeline and analogs thereof) and imidacloprid or one of its analogs, 5-methyl nicotinic acid, nicotinuric acid, aluminum nicotinate, nicoclonate, nicomol, niceritrol, oxiniacic acid, nicofuranose, acipimox (5-

methylpyrazine-2-carboxylic acid 4-oxide), Niaspan® (niacin extended-release tablets; Kos) and those which can be easily identified by one skilled in the art which bind to and agonize the HM74A or HM74 receptor (for example using the assays disclosed in Wise et al (2003) J. Biol. Chem 278:9869 (nicotine binding and [^{35}S]-GTPγS binding assays), Soga et al (2003) Biochem. Biophys. Res. Comm. 303:364 (radiolabel binding assay using the HM74 receptor which could be adapted to the HM74A receptor), Tunaru et al (2003) Nature Medicine 9:352 (calcium mobilization assay using the HM74 receptor which could be adapted to the HM74A receptor) and US6420183 (FLIPR assays are described generally in and may be adapted to the HM74A or HM74 receptor);

renin angiotensin system inhibitors;

bile acid reabsorption inhibitors (bile acid reuptake inhibitors), such as BARI 1453, SC435, PHA384640, S8921, AZD7706, and the like;

PPARδ agonists (including partial agonists) such as GW 501516, and GW 590735, and those disclosed in US5859051 (acetophenols), WO03/024395, W097/28149, WO01/79197, WO02/14291, WO02/46154, WO02/46176, WO02/076957, WO03/016291, WO03/033493, WO99/20275 (quinoline phenyl compounds), WO99/38845 (aryl compounds), WO00/63161 (1,4-disubstituted phenyl compounds), WO01/00579 (aryl compounds), WO01/12612, WO05/028453, & WO01/12187 (benzoic acid compounds), and WO97/31907 (substituted 4-hydroxy-phenylalconic acid compound);

sterol biosynthesis inhibitors such as DMP-565;

a sterol regulating element binding protein-I (SREBP-1) as disclosed in WO00/050574, for example, a sphingolipid, such as ceramide, or neutral sphingomyelenase (N-SMase) or fragment thereof;

triglyceride synthesis inhibitors;

microsomal triglyceride transport (MTTP or MTP) inhibitors, such as inplitapide, LAB687, 9-[4-[4-[[2-(2,2,2-Trifluoroethoxy)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, and CP346086, and those disclosed in US5595872; US5739135; US5712279; US5760246; US5827875; US5885983 and US5962440;

HMG-CoA reductase gene expression inhibitors (e.g., compounds that decrease HMG-CoA reductase expression by affecting (e.g., blocking) transcription or translation of HMG-CoA reductase into protein or compounds that may be biotransformed into compounds that have the aforementioned attributes by one or more enzymes in the cholesterol biosynthetic cascade or may lead to the accumulation of an isoprene metabolite that has the aforementioned activities (such regulation is readily determined by those skilled in the art according to standard assays (Methods of Enzymology, 110:9-19 1985))) such as those disclosed in US5041432 (certain 15-substituted lanosterol derivatives) and E. I. Mercer (1993) Prog. Lip. Res. 32:357 (oxygenated sterols that suppress the biosynthesis of HMG-CoA reductase);
squalene epoxidase inhibitors such as NB-598 ((E)-N-ethyl-N-(6,6-dimethyl-2-hepten-4-y- nyl)-3-[(3,3'-bithiophen-5-yl)methoxy]benzene-methanamine hydrochloride);
low density lipoprotein (LDL) receptor inducers such as MD-700 (Taisho Pharmaceuticals, LY295427 (Eli Lilly), HOE-402 (an imidazolidinyl-pyrimidine derivative that directly stimulates LDL receptor activity, see Huettinger et al (1993) Arterioscler. Thromb. 13:1005);
platelet aggregation inhibitors;
5-LO or FLAP inhibitors;
PPAR-α activators such as 2,4-dichlorophenoxyacetic acid, 2,4,5-trichlorophenoxyacetic acid, 2-methyl-4-chlorophenoxyacetic acid, 2-phenoxy-2-methylpropanoic acid ethyl ester, 2-(4-bromophenoxy)-2-methylpropanoic acid ethyl ester, 2-(4-iodophenoxy)-2-methylpropanoic acid ethyl ester, 2-(2-chlorophenoxy)-2-methylpropanoic acid ethyl ester, 2-(3-chlorophenoxy)-2-methylpropanoic acid ethyl ester, 2-(4-chlorophenoxy)-2-methylpropanoic acid ethyl ester, 2-(4-(4-chlorophenyl)phenoxy)-2-methylpropanoic acid ethyl ester, 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoic acid isopropyl ester, 2-(4-(2,2-dichlorocyclopropyl)phenoxy)-2-methylpropanoic acid, 2-(4-(4-chlorobenzoylaminoethyl)phenoxy)-2-methylpropanoic acid, 2-(2, 3-dimethyl-4-(1,2,3 ,4-tetrahydronaphth-1-yl)phenoxy)acetic acid, 2-(2-methyl-3-ethyl-4-(4-chlorobenzyl)phenoxy)acetic acid, (4-chloro-6-(2,3-xylidino)-2-pyrimidinyl)thioacetic acid, 2-((4-chloro-6-(2,3-xylidino)-2-pyrimidinyl)thioacetamido)ethanol, perfluoro-n-

decanoic acid, di-(2-ethylhexyl)adipate, di-(2-ethylhexyl)phosphate, di-(2-ethylhexyl)sebacate, bis-(carboxymethylthio)-1,10-decane, ethyl 4-(4-chlorophenoxy)butanoate, 2-(2-nitro-5-(2-chloro-4-trifluoromethylphenoxy)benzoyloxy)propanoic acid ethyl ester, 2-(4-(4-chlorobenzoyl))phenoxy-2-(2-methylpropionamido)ethylsulfonic acid, tetradecyloxyacetic acid, tetradecyloxypropionic acid, perfluorobutanoic acid, perfluorooctanoic acid, tetradecylthioacetic acid, tetradecylthiopropionic acid, di-(2-ethylhexyl)phthalate, mono-(2-ethylhexyl)phthalate, 2-ethylhexanoic acid, 2-propylhexanoic acid, compounds described in WO04010992, WO04/010936 (such as 5- {3- [2-Chloro-4- (2, 2, 2-trifluoro-ethoxy)-phenoxy]-propoxy}-2-methyl- 2, 3-dihydro-benzofuran-2-carboxylic acid, 5- {3- [4- (2, 2-Dimethyl-propyl)-2-propyl-phenoxy]-propoxy}-2-methyl- 2, 3-dihydro-benzofuran-2-carboxylic acid, 5- [3- (2-Chloro-4-trifluoromethoxy-phenoxy)-propoxy]-2-methyl-2, 3- dihydro-benzofuran-2-carboxylic acid, 5- {3- [4- (2, 2-Dimethyl-propyl)-2-propyl-phenoxy]-propoxy}-2-ethyl-2, 3- dihydro-benzofuran-2-carboxylic acid, 2-Ethyl-5- [3- (2-propyl-4-trifluoromethylsulfanyl-phenoxy)-propoxy]-2, 3- dihydro-benzofuran-2-carboxylic acid. 65- [3- (2-Chloro-4-trifluoromethylsulfanyl-phenoxy)-propoxy]-2-ethyl-2, 3-dihydro-benzofuran-2-carboxylic acid, 5- [3- (4-tert-Butyl-2-chloro-phenoxy)-propoxy]-2-ethyl-2, 3-dihydro- benzofuran-2-carboxylic acid, 5- [3- (2-Chloro-4-trifluoromethyl-phenoxy)-propoxy]-2-ethyl-2, 3-dihydro- benzofuran-2-carboxylic acid, 5- {3- [2-Chloro-4- (1, 1-dimethyl-propyl)-phenoxy]-propoxy}-2-ethyl-2, 3-dihydro-benzofuran-2-carboxylic acid, (2S)-5- [3- (2-Chloro-4-trifluoromethoxy-phenoxy)-propoxy]-2-ethyl-2, 3- dihydro-benzofuran-2-carboxylic acid, (2S)-5- {3- [2-Chloro-4- (2, 2-dimethyl-propyl)-phenoxy]-propoxy}-2- ethyl-2,3-dihydro-benzofuran-2-carboxylic acid, (2S)-5- {3- [2-Chloro-4- (2, 2, 2-trifluoro-ethoxy)-phenoxy]-propoxy}-2- ethyl-2,3-dihydro-benzofuran-2-carboxylic acid, (2S)-5- {3- [2-Chloro-4- (3, 3, 3-trifluoro-propyl)-phenoxy]-propoxy}-2- ethyl-2,3-dihydro-benzofuran-2-carboxylic acid, (2S)-5- {3- [2-Chloro-4- (2, 2, 2-trifluoro-ethyl)-phenoxy]-propoxy}-2- ethyl-2,3-dihydro-benzofuran-2-carboxylic acid, 6- [3- (2-Chloro-4-trifluoromethoxy-phenoxy)-propoxy]-2-ethyl-2, 3- dihydro-benzofuran-2-carboxylic acid, (2S)-5- [4- (2-Chloro-4-trifluoromethoxy-phenyl)-butoxy]-2-ethyl-2,

3- dihydro-benzofuran-2-carboxylic acid, (2R)-5- {3- [2-Chloro-4- (2, 2-dimethyl-propyl)-phenoxy]-propoxy}-2- isopropyl-2,3-dihydro-benzofuran-2-carboxylic acid, (2R)-5- [3- (2-Chloro-4-trifluoromethoxy-phenoxy)-propoxy]-2- isopropyl-2,3-dihydro-benzofuran-2-carboxylic acid, (2R)-5-{3-[2-Chloro4-(2, 2, 2-trifluoro-ethyl)-phenoxy]-propoxy}-2- isopropyl-2,3-dihydro-benzofuran-2-carboxylic acid, (2R)-5-[4- (2-Chloro-4-trifluoromethoxy-phenoxy)-butyl]-2-isopropyl- 2,3-dihydro-benzofuran-2-carboxylic acid, (2R)-2-tert-Butyl-5- {3- [2-chloro-4- (2, 2, 2-trifluoro-ethyl)-phenoxy]- propoxy}-2, 3-dihydro-benzofuran-2-carboxylic acid, 5- {3- [2-Chloro-4- (2, 2, 2-trifluoro-ethyl)-phenoxy]-propoxy}-2- trifluoromethyl-2, 3-dihydro-benzofuran-2-carboxylic acid, (2R)-5- [2-(2-Chloro-4-trifluoromethoxy-phenoxy)-ethoxy]-2-isopropyl- 2,3-dihydro-benzofuran-2-carboxylic acid, and (2R)-2-tert-Butyl-5- [2- (2-chloro-4-trifluoromethoxy-phenoxy)-ethoxy]- 2,3-dihydro-benzofuran-2-carboxylic acid).

[00116] PPAR modulators (including compounds that may have multiple functionality for activating various combinations of PPARα, PPARγ, and PPARδ) such as those disclosed in US6008237, US6248781, US6166049, WO00/12491, WO00/218355, WO00/23415, WO00/23416, WO00/23425, WO00/23442, WO00/23445, WO00/23451, WO00/236331, WO00/236332, WO00/238553, WO00/50392, WO00/53563, WO00/63153, WO00/63190, WO00/63196, WO00/63209, WO00/78312, WO00/78313, WO01/04351, WO01/14349, WO01/14350, WO01/16120, WO01/17994, WO01/21181, WO01/21578, WO01/25181, WO01/25225, WO01/25226, WO01/40192, WO01/79150, WO02/081428, WO02/100403, WO02/102780, WO02/79162, WO03/016265, WO03/033453, WO03/042194, WO03/043997, WO03/066581, WO97/25042, WO99/07357, WO99/11255, WO99/12534, WO99/15520, WO99/46232, and WO98/05331 (including GW2331 or (2-(4-[difluorophenyl]-1 heptylureido)ethyl]phenoxy)-2-methylbutyric));

lipoxygenase inhibitors including 15-lipoxygenase (15-LO) inhibitors such as those disclosed in WO97/12615 (benzimidazole derivatives), WO97/12613, WO96/38144 (isothiazolones), Sendobry et al. Brit. J. Pharmacology (1997) 120, 1199-1206, and Cornicelli et al, Current Pharmaceutical Design, 1999, 5, 11-20;

niacin-bound chromium, as disclosed in WO03/039535;

substituted acid derivatives disclosed in WO03/040114;

apolipoprotein B inhibitors such as those disclosed in WO02/090347, WO02/28835, WO03/045921, WO03/047575;

Factor Xa modulators such as those disclosed in WO03/047517, WO03/047520, WO03/048081;

ileal bile acid transport ("IBAT") inhibitors (or apical sodium co-dependent bile acid transport ("ASBT") inhibitors) such as benzothiepines (including 1,2-benzothiazepines; 1,4- benzothiazepines; 1,5-benzothiazepines; 1,2, 5-benzothiadiazepines);

IBAT inhibitors include but are not limited to compounds (e.g., those in claim 1 and the named examples) described in WO93/16055, WO94/18183, WO94/18184, WO96/05188, WO96/08484, WO96/16051, WO97/33882, WO98/38182, WO99/35135, WO98/40375, WO99/64409, WO99/64410, WO00/01687, WO00/47568, WO00/61568, DE 19825804, WO00/38725, WO00/38726, WO00/38727 (including those compounds with a 2,3,4,5-tetrahydro-1-benzothiepine 1,1-dioxide structure), WO00/38728, WO00/38729, WO01/66533, WO02/50051, EP0864582 (e.g., (3R, 5R)-3- butyl-3-ethyl-1,1-dioxido-5-phenyl-2, 3,4, 5-tetrahydro-1,4-benzothiazepin-8-yl (β-D- glucopyranosiduronic acid, WO94/24087, W098/07749, WO98/56757, WO99/32478, WO99/35135, WO00/20392, WO00/20393, WO00/20410, WO00/20437, WO01/34570, WO00/35889, WO01/68637, WO01/68096, WO02/08211, WO03/020710, WO03/022825, WO03/022830, WO03/022286, JP10072371, US5070103, EP251315, EP417725, EP489423, EP549967, EP573848, EP624593, EP624594, EP624595, EP869121 and EP1070703; S-8921 (disclosed in EP597107); 1,1-dioxo-3, 3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-1'-phenyl-1'-[N'-(carboxymethyl) carbamoyl] methyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-(carboxymethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-1'-phenyl-1'-[N'-(2-sulphoethyl) carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-

dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-1'-phenyl-1'-[N'-(2-sulphoethyl) carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-(2-sulphoethyl) carbamoyl]-4- hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-(2-carboxyethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-(2-carboxyethyl)carbamoyl]-4- hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-(5-carboxypentyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibuty1-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-(2-carboxyethyl)carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{a-[N'-(2-sulphoethyl)carbamoyl]-2-fluorobenzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-(R)-(2-hydroxy-1-carboxyethyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{N-[(R)-α-(N'-{(R)-1-[N"-(R)-(2-hydroxy-1- carboxyethyl)carbamoyl]-2-hydroxyethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8- (N-{a-[N'-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{a-[N'-((ethoxy)(methyl)phosphoryl-methyl)carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-{N-[(R)-α-(N'-{2-[(hydroxy)(methyl)phosphoryl]ethyl} carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-

dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-(2-methylthio-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{N-[(R)-α-(N'-{2-[(methyl)(ethyl)phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy}-2, 3,4,5-tetrahydro-1,5- benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{N-[(R)-α-(N'-{2-[(methyl)(hydroxy)phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl] carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[(R)-N'-(2-methylsulphinyl-1-carboxyethyl) carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; and 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methoxy-8-[N-{(R)-α-[N'-(2-sulphoethyl)carbamoyl]-4- hydroxybenzyl}carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine; compounds disclosed in claims 1-10 and examples 1-44 of WO03/020710; compounds disclosed in WO03/020710 (including 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-(2-(S)-3-(R)-4-(R)-5-(R)-2,3, 4,5, 6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1, 5-benzothiazepine; 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carbamoyl-2-hydroxyethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-(hydroxycarbamoyl-methyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[N ((R)-α-{N'-[2- (N'-pyrimidin-2- ylureido)ethyl] carbamoyl}benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8- [N-((R)-α-{N'-[2- (N'-pyridin-2-ylureido)ethyl]carbamoyl}benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N- {(R)-α-[N'-(l-t- butoxycarbonylpiperidin-4-ylmethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5- tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8- (N- {(R)-α-[N'-(2,3-

dihydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[N-((R)-α-{N'-[2-(3,4-dihydroxyphenyl)-2-methoxyethyl]carbamoyl}benzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5- benzothiazepine 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-(2-aminoethyl)carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-(piperidin-4-ylmethyl)carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; and 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N{(R)-α-[N'-(2-N, N-dimethylaminosulphamoylethyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine); compounds disclosed in claims 1-8 and examples 1-7 of WO03/022825; compounds disclosed in WO03/022825 (including 1-dioxo-3(R)-3-butyl-3-ethyl-5-(R)-5-phenyl-8-[N-((R)-α-carboxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,4-benzothiazepine; 1,1-dioxo-3(S)-3-butyl-3-ethyl-5-(S)-5-phenyl-8-[N-((R)-α-carboxybenzyl)carbamoylmethoxy] -2,3,4,5-tetrahydro-1,4-benzothiazepine; 1,1-dioxo-3(R)-3-butyl-3-ethyl-5-(R)-5-phenyl-8- (N-{(R)-α-[N-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1, 4-benzothiazepine; 1,1-dioxo-3(S)-3-butyl-3-ethyl-5-(S)-5-phenyl-8-(N-{(R)-α-[N-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine; 3,5-trans-1,1-dioxo-3-ethyl-3-butyl-5-phenyl-7-bromo-8-(N-{(R)-α-[N- (carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine; 3,5-trans-1,1-dioxo-3-(S)-3-ethyl-3-butyl-4-hydroxy-5-(S)-5-phenyl-7-bromo-8-(N-{(R)-α-[N-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4- benzothiazepine 3,5-trans-1,1-dioxo-3-(R)-3-ethyl-3-butyl-4-hydroxy-5-(R)-5-phenyl-7-bromo-8-(N-{(R)-α-[N-(carboxymethyl)carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine; 3,5-trans-l,1-dioxo-3-ethyl-3-butyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-(carboxymethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4- benzothiazepine; 3,5-trans-1,1-dioxo-3-ethyl-3-butyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-(2-sulphoethyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine ammonia salt; 1,1-dioxo-3-(S)-3-ethyl-3-butyl-5-(S)-5-phenyl-7-

methylthio-8-(N-{(R)-α-[N- (carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4- benzothiazepine diethylamine salt; and 1,1-dioxo-3-(R)-3-ethyl-3-butyl-5-(R)-5-phenyl-7-methylthio-8-(N- {(R)-α-[N-(carboxymethyl)carbamoyl]benzyl carbamoylmethoxy)-2, 3,4,5-tetrahydro-1,4-benzothiazepine diethylamine salt); compounds disclosed in claims 1-8 and examples 1-4 of WO03/022830; compounds disclosed in WO03/022830 (including 1,1-dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-(N-{(R)-α-[N-(carboxymethyl)carbamoyl]benzyl} carbamoylmethylthio)-2,3,4,5-tetrahydrobenzothiepine 1,1-dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-(N-{(R)-α-[N-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethylthio)-2,3,4,5-tetrahydrobenzothiepine ammonia salt 1,1-dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-{N-[a-(carboxy)-2-fluorobenzyl]carbamoylmethylthio}-2, 3,4,5-tetrahydrobenzothiepine; and 1,1-dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-{N-[1-(carboxy)-1-(thien-2-yl)methyl]carbamoylmethylthio}-2,3,4,5-tetrahydrobenzothiepine); compounds disclosed in claims 1-10 and examples 1-30 WO03/0222861; compounds disclosed in WO03/0222861 (including 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8- (N-{(R)-α-[N((R)-l-carboxy-2-methylthioethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5- benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-((S)-1-carboxy-2-(R)- hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1, 2,5-benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-((S)-l-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4, 5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-((S)-1-carboxybutyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4, 5-tetrahydro-1,2,5- benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-((S)-l-carboxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-((S)-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-((S)-1-carboxy-2-(R)-

hydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8- (N-{(R)-α-[N-((S)-1-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-((R)-1-carboxy-2-methylthioethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-{(S)-1-[N-((S)-2-hydroxy-1-carboxyethyl)carbamoyl]propyl}carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-((S)-1-carboxy-2-methylpropyl)carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-dioxo-3, 3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; and 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)-α-carboxy-4-hydroxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine); compounds having the structure of formula (EI) on page 58 of WO04/005247 (including 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-(2-(S)-3-(R)-4-(R)-5-(R)-2,3, 4,5, 6-pentahydroxyhexyl) carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R/S)-α-{N-[1-(R)-2-(S)-1-hydroxy-1-(3,4-dihydroxyphenyl)prop-2-yl]carbamoyl} benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (both enantiomers); 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{N-[(R)-α-(N-{2-(S)-[N-(carbamoylmethyl)carbamoyl]pyrrolidin-1-ylcarbonylmethyl}carbamoyl)benzyl] carbamoylmethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-Dioxo-3,3-bidutyl-5-phenyl-7-methylthio-8-[N-((R)-α-{N-[2-(3,4,5-

trihydroxyphenyl)ethyl]carbamoyl} benzyl)carbamoylmethoxy] -2,3,4,5-tetrahydro-1,2,5- benzothiadiazepine; and 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-(2 (R)-3-(S)-4-(S)-5-(R)-3,4,5,6-tetrahydroxytetrahydropyran-2-ylmethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine); compounds having the structure of formula (FI) on page 62 of WO04/005247 including (1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-l-carboxyethyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxypropyl) carbamoyl]benzyl}carbamoylemthoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxybutyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxy-2- methylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxy-2- methylbutyl)carbamoyl]benzyl}carbamoylemthoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxy-3-methylbutyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-l-carboxy-2-hydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1, 5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-l-carboxy-2-mesylethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxy-3-methylsulphonylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5- benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxy-3-mesylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-l-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-

tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxybutyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxyl-2-methylpropyl)carbamoyl]-4-hydroxybenzyl carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5- benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N- {(R)-α-[N'-((S)-1-carboxy-2-methylbutyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5- benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxy-3-methylbutyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5- benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxy-2-hydroxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5- benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxy-2-hydroxypropyl)carbamoyl]-4-hydroxybenzylcarbamoylemthoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3, 3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxy-2-methylthioethyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5- benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxy-2-methylsulphinylethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2, 3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N- {(R)-α-[N'-((S)-1-carboxy-2-mesylethyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxy-2-methoxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3, 3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxy-3-methylthiopropyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5- benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxy-3-methylsulphonylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2, 3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxy-3-mesylpropyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-

phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; and 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxyethyl) carbamoyl]benzyl}carbamoylemthoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine); compounds having the structure of formula (GI) on page 65 of WO04/005247 (including (+/-)-trans-1,1-dioxo-3-ethyl-3-butyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine; (+/-)-trans-1,1-dioxo-3-ethyl-3-butyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl) carbamoyl]benzyl carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine; 1,1-dioxo-3-ethyl-3-butyl-4-hydroxy-5-phenyl-7-(N-{a,-[N'-(2-(S)-3-(R)-4-(R)-5-(R)-2,3, 4,5,6-pentahydroxyhexyl)carbamoyl]-2-fluorobenzyl}carbamoylmethylthio)-2,3,4,5-tetrahydrobenzothiapine; and 1,1-dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-(N-{1-[N'- (2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]-1-(cyclohexyl)methyl icarbamoylmethylthio)-2,3,4,5-tetrahydrobenzothiepine); compounds disclosed as having IBAT activity disclosed in WO04/005247; compounds disclosed as having IBAT activity in Drugs of the Future, 24, 425-430 (1999); or a pharmaceutically acceptable salt, solvate, solvate of such salt or prodrug thereof;

ATP citrate lyase inhibitors including those disclosed in US5447954;

PPARδ activators such as disclosed in WO01/00603 (thiazole and oxazole derivates (e.g., CAS RN 317318-32-4), WO97/28149 (fluoro, chloro and thio phenoxy phenylacetic), US5093365 (non-1-oxidizable fatty acid analogues), and WO99/04815; and

other dyslipidemic agents such as benfluorex, β-Benzylbutyraimde, colmestrone, detaxtran, dextran sulphate sodium, eicosopentanoic acid, eritadenine, furazabol, meglutol, γ-Oryzanol, pantethine and derivatives thereof (as disclosed, for example, in US20050101565), pentaerythritol tetraacetate, α-phenylbutyramide, pirozadil, sultosilic acid, tiadenol, triparanol, and xenbucin, isoniazid (disclosed in WO97/35576), a lanosterol demethylase inhibitor (as disclosed in WO97/48701),

cholestagel (Sankyo/Geltex), lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphosphorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), nitric oxide synthase isoforms (e.g., endothelial (eNOS), neuronal (nNOS) and inducible (iNOS), for example purified, recombinant or viraly/retrovirally expressed), the antisense oligonucleotides described in Kipshidze, et al., J. Am. Coll. Cardio. 39(10):1686-1691 (2002); the nuclear targeted lacZ- and TIMP-1-encoding adenoviruses coupled to peptide-motif (HWGF) described in Turunen, et al., Mol Ther 6(3):306 (2002), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (disubstituted urea derivatives), compounds or combinations of compounds that result in the production or enhancement of nitric oxide (for example those disclosed in WO04091626, paragraphs 46-53), acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin, poly(diallylmethylamine) derivatives such as disclosed in US4759923, quaternary amine poly(diallyldimethylammonium chloride), pancreatic cholesteryl hydrolase (pCEH) inhibitors (such as WAY-121898), fish oil (which contains Omega 3 fatty acids (3-PUFA)), combinations of one or more anti-microbial agents (e.g., tetracyclin, ofloxacin, clinafloxacin, ciprofloxacin, clindamycin, doxycycline and minocycline, erythromycin or azalides such as trythromycin, roxithromycin, zithromycin, clarithromycin and azithromycin) with one or more metal chelators (e.g., desferrioxamine mesylate, haem derivatives, penicillamine, tiopronin, trientine, dihydrochloride, diethyldithiocarbamate, acetylsalicylic acid, disodium/trisodium, edetate, edetic acid, unithiol, copper chelators (penicillamine, tiopronin, trientine, dihydrochloride, diethyldithiocarbamate, acetylsalicylic acid)) as described in WO05034962, antisense inhibitors of apolipoprotein B (such as those disclosed in WO03097662, WO04044181, WO06020676 including ISIS 301012 (CAS RN 629167-92-6)), and ionenes such as disclosed in US4027009. Tests showing the efficacy of the therapy and the rationale for the combination therapy with a dyslipidemic agent are presented in US20030069221 (wherein the dyslipidemic agents are called 'cardiovascular agents').

Anti-diabetic agents

[00117] The compounds described herein can be used in therapeutic combination with one or more anti-diabetic agents, including but not limited to:

PPARγ agonists such as glitazones (e.g., WAY-120,744, AD 5075, balaglitazone, ciglitazone, darglitazone (CP-86325, Pfizer), englitazone (CP-68722, Pfizer), isaglitazone (MIT/J&J), MCC-555 (Mitsibishi disclosed in US5594016), pioglitazone (such as such as Actos™ pioglitazone; Takeda), rosiglitazone (Avandia™;Smith Kline Beecham), rosiglitazone maleate, troglitazone (Rezulin®, disclosed in US4572912), rivoglitazone (CS-011, Sankyo), GL-262570 (Glaxo Welcome), BRL49653 (disclosed in WO98/05331), CLX-0921, 5-BTZD, GW-0207, LG-100641, JJT-501 (JPNT/P&U), L-895645 (Merck), R-119702 (Sankyo/Pfizer), NN-2344 (Dr. Reddy/NN), YM-440 (Yamanouchi), LY-300512, LY-519818, R483 (Roche), T131 (Tularik), and the like and compounds disclosed in US4687777, US5002953, US5741803, US5965584, US6150383, US6150384, US6166042, US6166043, US6172090, US6211205, US6271243, US6288095, US6303640, US6329404, US5994554, W097/10813, WO97/27857,WO97/28115,WO97/28137,WO97/27847, WO00/76488, WO03/000685,WO03/027112,WO03/035602, WO03/048130,WO03/055867, and pharmaceutically acceptable salts thereof;

biguanides such as metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride, such as Glucophage™, Bristol-Myers Squibb); metformin hydrochloride with glyburide, such as Glucovance™, Bristol-Myers Squibb); buformin (Imidodicarbonimidic diamide, N-butyl-); etoformine (1-Butyl-2-ethylbiguanide, Schering A. G.); other metformin salt forms (including where the salt is chosen from the group of, acetate, benzoate, citrate, ftimarate, embonate, chlorophenoxyacetate, glycolate, palmoate, aspartate, methanesulphonate, maleate, parachlorophenoxyisobutyrate, formate, lactate, succinate, sulphate, tartrate, cyclohexanecarboxylate, hexanoate, octanoate, decanoate, hexadecanoate, octodecanoate, benzenesulphonate, trimethoxybenzoate, paratoluenesulphonate, adamantanecarboxylate, glycoxylate, glutarnate, pyrrolidonecarboxylate, naphthalenesulphonate, 1-glucosephosphate, nitrate, sulphite, dithionate and phosphate), and phenformin;

protein tyrosine phosphatase-1B (PTP-1B) inhibitors, such as A-401,674, KR 61639, OC-060062, OC-83839, OC-297962, MC52445, MC52453, ISIS 113715, and those disclosed in WO99/585521, WO99/58518, WO99/58522, WO99/61435, WO03/032916, WO03/032982, WO03/041729, WO03/055883, WO02/26707, WO02/26743, JP2002114768, and pharmaceutically acceptable salts and esters thereof;

sulfonylureas such as acetohexamide (e.g., Dymelor, Eli Lilly), carbutamide, chlorpropamide (e.g., Diabinese®, Pfizer), gliamilide (Pfizer), gliclazide (e.g., Diamcron, Servier Canada Inc), glimepiride (e.g., disclosed in US4379785, such as Amaryl™, Aventis), glipentide, glipizide (e.g., Glucotrol or Glucotrol XL Extended Release, Pfizer), gliquidone, glisolamide, glyburide/glibenclamide (e.g., Micronase or Glynase Prestab, Pharmacia & Upjohn and Diabeta, Aventis), tolazamide (e.g., Tolinase), and tolbutamide (e.g., Orinase), and pharmaceutically acceptable salts and esters thereof;

meglitinides such as repaglinide (e.g., Pranidin®, Novo Nordisk), KAD1229 (PF/Kissei), and nateglinide (e.g., Starlix®, Novartis), and pharmaceutically acceptable salts and esters thereof;

α glucoside hydrolase inhibitors (or glucoside inhibitors) such as acarbose (e.g., Precose™, Bayer disclosed in US4904769), miglitol (such as Glyset™, Pharmacia & Upjohn disclosed in US4639436), camiglibose (Methyl 6-deoxy-6-[(2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidino]-alpha-D-glucopyranoside, Marion Merrell Dow), voglibose (Takeda), adiposine, emiglitate, pradimicin-Q, salbostatin, CKD-711, MDL- 25,637, MDL-73,945, and MOR 14, and the compounds disclosed in US4062950, US4174439, US4254256, US4701559, US4639436, US5192772, US4634765, US5157116, US5504078, US5091418, US5217877, US51091 and WO01/47528 (polyamines);

α-amylase inhibitors such as tendamistat, trestatin, and A1-3688, and the compounds disclosed in US4451455, US4623714, and US4273765;

SGLT2 inhibtors including those disclosed in US6414126 and US6515117;

an aP2 inhibitor such as disclosed in US6548529;

insulin secreatagogues such as linogliride, A-4166, forskilin, dibutyrl cAMP,

isobutylmethylxanthine (IBMX), and pharmaceutically acceptable salts and esters thereof;

fatty acid oxidation inhibitors, such as clomoxir, and etomoxir, and pharmaceutically acceptable salts and esters thereof;

A2 antagonists, such as midaglizole, isaglidole, deriglidole, idazoxan, earoxan, and fluparoxan, and pharmaceutically acceptable salts and esters thereof;

insulin and related compounds (e.g., insulin mimetics) such as biota, LP-100, novarapid, insulin detemir, insulin lispro, insulin glargine, insulin zinc suspension (lente and ultralente), Lys-Pro insulin, GLP-1 (1-36) amide, GLP-1 (73-7) (insulintropin, disclosed in US5614492), LY-315902 (Lilly), GLP-1 (7-36)-NH2), AL-401 (AutoImmune), certain compositions as disclosed in US4579730, US4849405, US4963526, US5642868, US5763396, US5824638, US5843866, US6153632, US6191105, and WO 85/05029, and primate, rodent, or rabbit insulin including biologically active variants thereof including allelic variants, more preferably human insulin available in recombinant form (sources of human insulin include pharmaceutically acceptable and sterile formulations such as those available from Eli Lilly (Indianapolis, Ind. 46285) as Humulin™ (human insulin rDNA origin), also see the the physician's desk reference, 55.sup.th Ed. (2001) Medical Economics, Thomson Healthcare (disclosing other suitable human insulins);

non-thiazolidinediones such as JT-501 and farglitazar (GW-2570/GI- 262579), and pharmaceutically acceptable salts and esters thereof;

PPARα/γ dual agonists such as AR-HO39242 (Aztrazeneca), GW-409544 (Glaxo-Wellcome), BVT-142, CLX-0940, GW-1536, GW-1929, GW-2433, KRP-297 (Kyorin Merck; 5-[(2,4-Dioxo thiazolidinyl)methyl] methoxy-N-[[4-(trifluoromethyl)phenyl] methyl]benzamide), L-796449, LR-90, MK-0767 (Merck/Kyorin/Banyu), SB 219994, muraglitazar (BMS), tesaglitzar (Astrazeneca), reglitazar (JTT-501) and those disclosed in WO99/16758, WO99/19313, WO99/20614, WO99/38850, WO00/23415, WO00/23417, WO00/23445, WO00/50414, WO01/00579, WO01/79150, WO02/062799, WO03/004458, WO03/016265, WO03/018010, WO03/033481, WO03/033450, WO03/033453, WO03/043985, WO 031053976, U.S. application Ser. No. 09/664,598, filed Sep. 18,

2000, Murakami et al. Diabetes 47, 1841-1847 (1998), and pharmaceutically acceptable salts and esters thereof;

other insulin sensitizing drugs;

VPAC2 receptor agonists;

GLK modulators, such as those disclosed in WO03/015774;

retinoid modulators such as those disclosed in WO03/000249;

GSK 3β/GSK 3 inhibitors such as 4-[2-(2-bromophenyl)-4-(4-fluorophenyl-1H-imidazol-5-yl]pyridine and those compounds disclosed in WO03/024447, WO03/037869, WO03/037877, WO03/037891, WO03/068773, EP1295884, EP1295885, and the like;

glycogen phosphorylase (HGLPa) inhibitors such as CP-368,296, CP-316,819, BAYR3401, and compounds disclosed in WO01/94300, WO02/20530, WO03/037864, and pharmaceutically acceptable salts or esters thereof;

ATP consumption promotors such as those disclosed in WO03/007990;

TRB3 inhibitors;

vanilloid receptor ligands such as those disclosed in WO03/049702;

hypoglycemic agents such as those disclosed in WO03/015781 and WO03/040114;

glycogen synthase kinase 3 inhibitors such as those disclosed in WO03/035663 agents such as those disclosed in WO99/51225, US20030134890, WO01/24786, and WO03/059870;

insulin-responsive DNA binding protein-1 (IRDBP-1) as disclosed in WO03/057827, and the like;

adenosine A2 antagonists such as those disclosed in WO03/035639, WO03/035640, and the like;

PPARδ agonists such as GW 501516, GW 590735, and compounds disclosed in JP10237049 and WO02/14291;

dipeptidyl peptidase IV (DP-IV) inhibitors, such as isoleucine thiazolidide, NVP-DPP728A (1-[[[2-[(5-cyanopyridin-2-yl)amino]ethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine, disclosed by Hughes et al, Biochemistry, 38(36), 11597-11603, 1999), P32/98, NVP-LAF-237, P3298, TSL225 (tryptophyl-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid, disclosed by Yamada et al, Bioorg. & Med. Chem. Lett. 8 (1998)

1537-1540), valine pyrrolidide, TMC-2A/2B/2C, CD-26 inhibitors, FE999011, P9310/K364, VIP 0177, DPP4, SDZ 274-444, 2-cyanopyrrolidides and 4-cyanopyrrolidides as disclosed by Ashworth et al, Bioorg. & Med. Chem. Lett., Vol. 6, No. 22, pp 1163-1166 and 2745-2748 (1996) ,and the compounds disclosed in US6395767, US6573287, US6395767 (compounds disclosed include BMS-477118, BMS-471211 and BMS 538,305), WO99/38501, WO99/46272, WO99/67279, WO99/67278, WO99/61431WO03/004498, WO03/004496, EP1258476, WO02/083128, WO02/062764, WO03/000250, WO03/002530, WO03/002531, WO03/002553, WO03/002593, WO03/000180, and WO03/000181;
GLP-1 agonists such as exendin-3 and exendin-4 (including the 39 aa peptide synthetic exendin-4 called Exenatide®), and compounds disclosed in US2003087821 and NZ 504256, and pharmaceutically acceptable salts and esters thereof;
peptides including amlintide and Symlin® (pramlintide acetate); and
glycokinase activators such as those disclosed in US2002103199 (fused heteroaromatic compounds) and WO02/48106 (isoindolin-1-one-substituted propionamide compounds).

[00118] Showing the efficacy of the therapy and the rationale for the combination therapy with an anti-diabetic agent are presented in US20040214811.

Anti-hypertensive agents

[00119] The compounds described herein can be used in therapeutic combination with one or more anti-hypertensive agents, including but not limited to:
diuretics, such as thiazides (e.g., chlorthalidone, cyclothiazide (CAS RN 2259-96-3), chlorothiazide (CAS RN 72956-09-3, which may be prepared as disclosed in US2809194), dichlorophenamide, hydroflumethiazide, indapamide, polythiazide, bendroflumethazide, methyclothazide, polythiazide, trichlormethazide, chlorthalidone, indapamide, metolazone, quinethazone, althiazide (CAS RN 5588-16-9, which may be prepared as disclosed in British Patent No. 902,658), benzthiazide (CAS RN 91-33-8, which may be prepared as disclosed in US3108097), buthiazide (which may be prepared as disclosed in British Patent Nos. 861,367), and hydrochlorothiazide), loop diuretics (e.g., bumetanide, ethacrynic acid, furosemide, and torasemide), potassium

sparing agents (e.g., amiloride, and triamterene (CAS Number 396-01-0)), and aldosterone antagonists (e.g., spironolactone (CAS Number 52-01-7), epirenone, and the like);

β-adrenergic blockers such as Amiodarone (Cordarone, Pacerone), bunolol hydrochloride (CAS RN 31969-05-8, Parke-Davis), acebutolol (±N-[3-Acetyl-4-[2-hydroxy-3-[(1 methylethyl)amino]propoxy]phenyl]-butanamide, or (±)-3'-Acetyl-4'-[2-hydroxy -3-(isopropylamino) propoxy] butyranilide), acebutolol hydrochloride (e.g., Sectral®, Wyeth-Ayerst), alprenolol hydrochloride (CAS RN 13707-88-5 see Netherlands Patent Application No. 6,605,692), atenolol (e.g., Tenormin®, AstraZeneca), carteolol hydrochloride (e.g., Cartrol® Filmtab®, Abbott), Celiprolol hydrochloride (CAS RN 57470-78-7, also see in US4034009), cetamolol hydrochloride (CAS RN 77590-95-5, see also US4059622), labetalol hydrochloride (e.g., Normodyne®, Schering), esmolol hydrochloride (e.g., Brevibloc®,Baxter), levobetaxolol hydrochloride (e.g., Betaxon™ Ophthalmic Suspension, Alcon), levobunolol hydrochloride (e.g., Betagan® Liquifilm® with C CAP® Compliance Cap, Allergan), nadolol (e.g., Nadolol, Corgard, Mylan), practolol (CAS RN 6673-35-4, see also US3408387), propranolol hydrochloride (CAS RN 318-98-9), sotalol hydrochloride (e.g., Betapace AF™,Berlex), timolol (2-Propanol,1-[(1,1-dimethylethyl)amino]-3-[[4-4(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-, hemihydrate, (S)-, CAS RN 91524-16-2), timolol maleate (S)-1-[(1,1-dimethylethyl) amino]-3-[[4- (4-morpholinyl)-1,2,5-thiadiazol -3- yl] oxy]-2-propanol (Z)-2-butenedioate (1:1) salt, CAS RN 26921-17-5), bisoprolol (2-Propanol, 1-[4-[[2-(1-methylethoxy)ethoxy]-methyl]phenoxyl]-3-[(1-meth- ylethyl)amino]-, (±), CAS RN 66722-44-9), bisoprolol fumarate (such as (±)-1-[4-[[2-(1-Methylethoxy) ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol (E) -2-butenedioate (2:1) (salt), e.g., Zebeta™ , Lederle Consumer), nebivalol (2H-1-Benzopyran-2-methanol, αα'-[iminobis(methylene)]bis[6-fluoro-3,4-dihydro-, CAS RN 99200-09-6 see also U.S. Pat. No. 4,654,362), cicloprolol hydrochloride, such 2-Propanol, 1-[4-[2-(cyclopropylmethoxy)ethoxy]phenoxy]-3-[1-methylethyl)amino]-, hydrochloride, A.A.S. RN 63686-79-3), dexpropranolol hydrochloride (2-Propanol,1-[1-methylethy)-

amino]-3-(1-naphthalenyloxy)-hydrochloride (CAS RN 13071-11-9), diacetolol hydrochloride (Acetamide, N-[3-acetyl-4-[2-hydroxy-3-[(1-methyl-ethyl)amino]propoxy][phenyl]-, monohydrochloride CAS RN 69796-04-9), dilevalol hydrochloride (Benzamide, 2-hydroxy-5-[1-hydroxy-2-[1-methyl-3-phenylpropyl)amino]ethyl]-, monohydrochloride, CAS RN 75659-08-4), exaprolol hydrochloride (2-Propanol, 1-(2-cyclohexylphenoxy)-3-[(1-methylethyl)amino]-, hydrochloride CAS RN 59333-90-3), flestolol sulfate (Benzoic acid, 2-fluro-,3-[[2-[aminocarbonyl)amino]- -dimethylethyl]amino]-2-hydroxypropyl ester, (±)- sulfate (1:1) (salt), CAS RN 88844-73-9; metalol hydrochloride (Methanesulfonamide, N-[4-[1-hydroxy-2-(methylamino)propyl]phenyl]-, monohydrochloride CAS RN 7701-65-7), metoprolol 2-Propanol, 1-[4-(2-methoxyethyl)phenoxy]-3-[1-methylethyl)amino]-; CAS RN 37350-58-6), metoprolol tartrate (such as 2-Propanol, 1-[4-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]-, e.g., Lopressor®, Novartis), pamatolol sulfate (Carbamic acid, [2-[4-[2-hydroxy-3-[(1-methylethyl)amino]propoxyl]phenyl]-ethyl]-, methyl ester, (±) sulfate (salt) (2:1), CAS RN 59954-01-7), penbutolol sulfate (2-Propanol, 1-(2-cyclopentylphenoxy)-3-[1,1-dimethyle- thyl)amino]1, (S)-, sulfate (2:1) (salt), CAS RN 38363-32-5), practolol (Acetamide, N-[4-[2-hydroxy-3-[(1-methylethyl)amino]-propoxy]phenyl]-, CAS RN 6673-35-4;) tiprenolol hydrochloride (Propanol, 1-[(1-methylethyl)amino]-3-[2-(methylthio)-phenoxy]-, hydrochloride, (±), CAS RN 39832-43-4), tolamolol (Benzamide, 4-[2-[[2-hydroxy-3-(2-methylphenoxy)-propyl]amino]ethoxyl]-, CAS RN 38103-61-6), bopindolol, indenolol, pindolol (e.g., Visken), propanolol (e.g., Inderal, Inderal-LA), tertatolol, Coreg (carvedilol), and tilisolol, and the like; calcium channel blockers such as besylate salt of amlodipine (such as 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate, e.g., Norvasc®, Pfizer), clentiazem maleate (1,5-Benzothiazepin-4(5H)-one, 3-(acetyloxy)-8-chloro-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-(2S-cis)-, (Z)-2-butenedioate (1:1), see also US4567195), isradipine (3,5-Pyridinedicarboxylic acid, 4-(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-, methyl 1-methylethyl ester, (±)-4(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate, see also US4466972); nimodipine

(such as is isopropyl (2- methoxyethyl) 1, 4- dihydro -2,6- dimethyl -4- (3-nitrophenyl) -3,5- pyridine - dicarboxylate, e.g., Nimotop®, Bayer), felodipine (such as ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate- , e.g., Plendil® Extended-Release, AstraZeneca LP), nilvadipine (3,5-Pyridinedicarboxylic acid, 2-cyano-1,4-dihydro-6-methyl-4-(3-nitrophenyl)-,3-methyl 5-(1-methylethyl) ester, also see US3799934), nifedipine (such as 3,5-pyridinedicarboxylic acid,1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester, e.g., Procardia XL® Extended Release Tablets, Pfizer), diltiazem hydrochloride (such as 1,5-Benzothiazepin-4(5H)-one,3-(acetyloxy)-5[2-(dimethylamino)ethyl]-2,-3-dihydro-2(4-methoxyphenyl)-, monohydrochloride, (+)-cis., e.g., Tiazac®, Forest), verapamil hydrochloride (such as benzeneacetronitrile, (alpha)-[[3-[[2-(3,4-dimethoxyphenyl) ethyl]methylamino]propyl]-3,4-dimethoxy-(alpha)-(1-methylethyl) hydrochloride, e.g., Isoptin® SR, Knoll Labs), teludipine hydrochloride (3,5-Pyridinedicarboxylic acid, 2-[(dimethylamino)methyl]4-[2-[(1E)-3-(1,1-dimethylethoxy)-3-oxo-1-propenyl]phenyl]-1,4-dihydro-6-methyl-, diethyl ester, monohydrochloride) CAS RN 108700-03-4), belfosdil (Phosphonic acid, [2-(2-phenoxyethyl)-1,3-propane- diyl]bis-, tetrabutyl ester CAS RN 103486-79-9), fostedil (Phosphonic acid, [[4-(2-benzothiazolyl)phenyl]methyl]-, diethyl ester CAS RN 75889-62-2), aranidipine, azelnidipine, barnidipine, benidipine, bepridil, cinaldipine, clevidipine, efonidipine, gallopamil, lacidipine, lemildipine, lercanidipine, monatepil maleate (1-Piperazinebutanamide, N-(6,11-dihydrodibenzo(b,e)thiepin-11-yl)$_4$-(4-fluorophenyl)-, (±)-, (Z)-2-butenedioate (1:1) (±)-N-(6,11-Dihydrodibenzo(b,e)thiep-in-11-yl)-4-(p-fluorophenyl)-1-piperazinebutyramide maleate (1:1) CAS RN 132046-06-1), nicardipine, nisoldipine, nitrendipine, manidipine, pranidipine, and the like;
T-channel calcium antagonists such as mibefradil;
angiotensin converting enzyme (ACE) inhibitors such as benazepril, benazepril hydrochloride (such as 3-[[1-(ethoxycarbonyl)-3-phenyl-(1S)-propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H -1-(3S)-benzazepine-1-acetic acid monohydrochloride, e.g., Lotrel®, Novartis), captopril (such as 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline, e.g., Captopril, Mylan, CAS RN 62571-86-2 and others disclosed in US4046889), ceranapril (and others disclosed in US4452790), cetapril (alacepril,

Dainippon disclosed in Eur. Therap. Res. 39:671 (1986); 40:543 (1986)), cilazapril (Hoffman-LaRoche) disclosed in J. Cardiovasc. Pharmacol. 9:39 (1987), indalapril (delapril hydrochloride (2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-bicyclo[2.2.1]hept-5-en-2-yl-6-chloro-3,4-dihydro-, 1,1-dioxide CAS RN 2259-96-3); disclosed in US4385051), enalapril (and others disclosed in US4374829), enalopril, enaloprilat, fosinopril, ((such as *trans*-L-proline, 4-cyclohexyl-1-[[[2-methyl-1-(1-oxopropoxy) propoxy](4-phenylbutyl) phosphinyl]acetyl]-, sodium salt, e.g., Monopril, Bristol-Myers Squibb and others disclosed in US4168267), fosinopril sodium (L-Proline, 4-cyclohexyl-1-[[(R)-[(1S)-2-methyl-1-(1-ox- opropoxy)propox), imidapril, indolapril (Schering, disclosed in J. Cardiovasc. Pharmacol. 5:643, 655 (1983)), lisinopril (Merck), losinopril, moexipril, moexipril hydrochloride (3-Isoquinolinecarboxylic acid, 2-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,- 2,3,4-tetrahydro-6,7-dimethoxy-, monohydrochloride, (3S)- CAS RN 82586-52-5), quinapril, quinaprilat, ramipril (Hoechsst) disclosed in EP 79022 and Curr. Ther. Res. 40:74 (1986), perindopril erbumine (such as 2S,3aS,7aS-1-[(S)-N-[(S)-1-Carboxybutyl]alanyl]hexahydro-2-indolinecarboxylic acid, 1-ethyl ester, compound with tert-butylamine (1:1), e.g., Aceon®, Solvay), perindopril (Servier, disclosed in Eur. J. clin. Pharmacol. 31:519 (1987)), quanipril (disclosed in US4344949), spirapril (Schering, disclosed in Acta. Pharmacol. Toxicol. 59 (Supp. 5):173 (1986)), tenocapril, trandolapril, zofenopril (and others disclosed in US4316906), rentiapril (fentiapril, disclosed in Clin. Exp. Pharmacol. Physiol. 10:131 (1983)), pivopril, YS980, teprotide (Bradykinin potentiator BPP9a CAS RN 35115-60-7), BRL 36,378 (Smith Kline Beecham, see EP80822 and EP60668), MC-838 (Chugai, see C.A. 102:72588v and Jap. J. Pharmacol. 40:373 (1986), CGS 14824 (Ciba-Geigy, 3-([1-ethoxycarbonyl-3-phenyl-(1S)-propyl]amino)-2,3,4,5-tetrahydro-2-ox- o-1-(3S)-benzazepine-1 acetic acid HCl, see U.K. Patent No. 2103614), CGS 16,617 (Ciba-Geigy, 3(S)-[[(1S)-5-amino-1-carboxypentyl]amino]-2,3,4,- 5-tetrahydro-2-oxo-1H-1-benzazepine-1-ethanoic acid, see US4473575), Ru 44570 (Hoechst, see Arzneimittelforschung 34:1254 (1985)), R 31-2201 (Hoffman-LaRoche see FEBS Lett. 165:201 (1984)), CI925 (Pharmacologist 26:243, 266 (1984)), WY-44221 (Wyeth, see J. Med. Chem. 26:394 (1983)), and

those disclosed in US2003006922 (paragraph 28), US4337201, US4432971 (phosphonamidates);

neutral endopeptidase inhibitors such as omapatrilat (Vanlev®), CGS 30440, cadoxatril and ecadotril, fasidotril (also known as aladotril or alatriopril), sampatrilat, mixanpril, and gemopatrilat, AVE7688, ER4030, and those disclosed in US5362727, US5366973, US5225401, US4722810, US5223516, US4749688, US5552397, US5504080, US5612359, US5525723, EP0599444, EP0481522, EP0599444, EP0595610, EP0534363, EP534396, EP534492, EP0629627;

endothelin antagonists such as tezosentan, A308165, and YM62899, and the like;

vasodilators such as hydralazine (apresoline), clonidine (clonidine hydrochloride (1H-Imidazol-2-amine, N-(2,6-dichlorophenyl)4,5-dihydro-, monohydrochloride CAS RN 4205-91-8), catapres, minoxidil (loniten), nicotinyl alcohol (roniacol), diltiazem hydrochloride (such as 1,5-Benzothiazepin-4(5H)-one,3-(acetyloxy)-5[2-(dimethylamino)ethyl]-2,-3-dihydro-2(4-methoxyphenyl)-, monohydrochloride, (+)-cis, e.g., Tiazac®, Forest), isosorbide dinitrate (such as 1,4:3,6-dianhydro-D-glucitol 2,5-dinitrate e.g., Isordil® Titradose®, Wyeth-Ayerst), sosorbide mononitrate (such as 1,4:3,6-dianhydro-D-glucito- l,5-nitrate, an organic nitrate, e.g., Ismo®, Wyeth-Ayerst), nitroglycerin (such as 2,3 propanetriol trinitrate, e.g., Nitrostat® Parke-Davis), verapamil hydrochloride (such as benzeneacetonitrile, (±)-(alpha)[3-[[2-(3,4 dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-(alpha)- (1-methylethyl) hydrochloride, e.g., Covera HS® Extended-Release, Searle), chromonar (which may be prepared as disclosed in US3282938), clonitate (Annalen 1870 155), droprenilamine (which may be prepared as disclosed in DE2521113), lidoflazine (which may be prepared as disclosed in US3267104); prenylamine (which may be prepared as disclosed in US3152173), propatyl nitrate (which may be prepared as disclosed in French Patent No. 1,103,113), mioflazine hydrochloride (1-Piperazineacetamide, 3-(aminocarbonyl)4-[4,4-bis(4-fluorophenyl)butyl]-N-(2,6-dichlorophenyl)-, dihydrochloride CAS RN 83898-67-3), mixidine (Benzeneethanamine, 3,4-dimethoxy-N-(1-methyl-2-pyrrolidinylidene)- Pyrrolidine, 2-[(3,4-dimethoxyphenethyl)imino]-1-methyl-1-Methyl-2-[(3,4-dimethoxyphenethyl)imino]pyrrolidine CAS RN 27737-38-8), molsidomine (1,2,3-

Oxadiazolium, 5-[(ethoxycarbonyl)amino]-3-(4-morpholinyl)-, inner salt CAS RN 25717-80-0), isosorbide mononitrate (D-Glucitol, 1,4:3,6-dianhydro-, 5-nitrate CAS RN 16051-77-7), erythrityl tetranitrate (1,2,3,4-Butanetetrol, tetranitrate, (2R,3S)-rel- CAS RN 7297-25-8), clonitrate(1,2-Propanediol, 3-chloro-, dinitrate (7CI, 8CI, 9CI) CAS RN 2612-33-1), dipyridamole Ethanol, 2,2',2",2'"-[(4,8-di-1-piperidinylpyrimido[5,4-d]pyrimidine-2,6-diyl)dinitrilo]tetrakis- CAS RN 58-32-2), nicorandil (CAS RN 65141-46-0 3-), pyridinecarboxamide (N-[2-(nitrooxy)ethyl]-Nisoldipine3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, methyl 2-methylpropyl ester CAS RN 63675-72-9), nifedipine3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester CAS RN 21829-25-4), perhexiline maleate (Piperidine, 2-(2,2-dicyclohexylethyl)-, (2Z)-2-butenedioate (1:1) CAS RN 6724-53-4), oxprenolol hydrochloride (2-Propanol, 1-[(1-methylethyl)amino]-3-[2-(2-propenyloxy)phenoxy]-, hydrochloride CAS RN 6452-73-9), pentrinitrol (1,3-Propanediol, 2,2-bis[(nitrooxy)methyl]-, mononitrate (ester) CAS RN 1607-17-6), verapamil (Benzeneacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]- methylamino]propyl]-3,4-dimethoxy-α-(1-methylethyl)- CAS RN 52-53-9) and the like;

angiotensin II receptor antagonists such as, aprosartan, zolasartan, olmesartan, pratosartan, FI6828K, RNH6270, candesartan (1 H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]4-yl]methyl]- CAS RN 139481-59-7), candesartan cilexetil ((+/-)-l-(cyclohexylcarbonyloxy)ethyl-2-ethoxy-l-[[2'-(lH-tetrazol-5-yl)biphenyl-4-yl]-lH-benzimidazole carboxylate, CAS RN 145040-37-5, US5703110 and US5196444), eprosartan (3-[1-4-carboxyphenylmethyl)-2-n-butyl-imidazol-5-yl]-(2-thienylmethyl) propenoic acid, US5185351 and US5650650), irbesartan (2-n-butyl-3- [[2'-(lh-tetrazol-5-yl)biphenyl-4-yl]methyl]1,3-diazazspiro[4,4]non-l-en-4-one, US5270317 and US5352788), losartan (2-N-butyl-4-chloro-5-hydroxymethyl-l-[(2'-(lH-tetrazol-5-yl)biphenyl-4-yl)-methyl]imidazole, potassium salt, US5138069, US5153197 and US5128355), tasosartan (5,8-dihydro-2,4-dimethyl-8-[(2'-(lH-tetrazol-5-yl)[1,1'-biphenyl]4-yl)methyl]-pyrido[2,3-d]pyrimidin-7(6H)-one, US5149699), telmisartan (4'-[(1,4-dimethyl-2'-propyl-(2,6'-bi-lH-benzimidazol)-l'-yl)]-[1,1'-biphenyl]-2-carboxylic acid, CAS RN 144701-48-4,

US5591762), milfasartan, abitesartan, valsartan (Diovan® (Novartis), (S)-N-valeryl-N-[[2'-(lH-tetrazol-5-yl)biphenyl-4-yl)methyl]valine, US5399578), EXP-3137 (2-N-butyl-4-chloro-l-[(2'-(lH-tetrazol-5-yl)biphenyl-4-yl)-methyl]imidazole-5-carboxylic acid, US5138069, US5153197 and US5128355), 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine, 4'[2-ethyl-4-methyl-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-2-yl]-benzimidazol-1-yl]-methyl]-1,1'-biphenyl]-2- carboxylic acid, 2-butyl-6-(1-methoxy-1-methylethyl)-2-[2'-)IH-tetrazol-5-yl)biphenyl-4-ylmethyl]guinazolin-4(3H)-one, 3-[2'-carboxybiphenyl-4-yl)methyl]-2-cyclopropyl-7-methyl- 3H-imidazo[4,5-b]pyridine, 2-butyl-4-chloro-1-[(2'-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-carboxylic acid, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-carboxylic acid-1-(ethoxycarbonyl-oxy)ethyl ester potassium salt, dipotassium 2-butyl-4-(methylthio)-1-[[2-[[[(propylamino)carbonyl]amino]-sulfonyl](1,1'-biphenyl)-4-yl]methyl]-1H-imidazole-5-carboxylate, methyl-2-[[4-butyl-2-methyl-6-oxo-5-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-1-(6H)-pyrimidinyl]methyl]-3-thiophencarboxylate, 5-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl]-2-[2-(1H-tetrazol-5-ylphenyl)]pyridine, 6-butyl-2-(2-phenylethyl)-5[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-methyl]pyrimidin-4-(3H)-one D,L lysine salt, 5-methyl-7-n-propyl-8-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-[1,2,4]-triazolo[1,5-c]pyrimidin-2(3H)-one, 2,7-diethyl-5-[[2'-(5-tetrazoly)biphenyl-4-yl]methyl]-5H-pyrazolo[1,5-b][1,2,4]triazole potassium salt, 2-[2-butyl-4,5-dihydro-4-oxo-3-[2'-(1H-tetrazol-5-yl)-4-biphenylmethyl]-3H-imidazol[4,5-c]pyridine-5-ylmethyl]benzoic acid, ethyl ester, potassium salt, 3-methoxy-2,6-dimethyl-4-[[2'(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methoxy]pyridine, 2-ethoxy-1-[[2'-(5-oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid, 1-[N-(2'-(1H-tetrazol-5-yl)biphenyl-4-yl-methyl)-N-valerolylaminomethyl)cyclopentane-1-carboxylic acid, 7-methyl-2n-propyl-3-[[2'1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-3H-imidazo[4,5-6]pyridine, 2-[5-[(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine-3-yl)methyl]-2-quinolinyl]sodium benzoate, 2-butyl-6-chloro-4-hydroxymethyl-5-methyl-3-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]pyridine, 2-[[[2-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoic acid tetrazol-5-yl)biphenyl-4-yl]methyl]pyrimidin-6-one,

4(S)-[4-(carboxymethyl)phenoxy]-N-[2(R)-[4-(2-sulfobenzamido)imidazol-1-yl]octanoyl]-L-proline, 1-(2,6-dimethylphenyl)-4-butyl-1,3-dihydro-3-[[6-[2-(1H-tetrazol-5-yl)phenyl]-3-pyridinyl]methyl]-2H-imidazol-2-one, 5,8-ethano-5,8-dimethyl-2-n-propyl-5,6,7,8-tetrahydro-1-[[2'(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H,4H-1,3,4a,8a-tetrazacyclopentanaphthalene-9-one, 4-[1-[2'-(1,2,3,4-tetrazol-5-yl)biphen-4-yl)methylamino]-5,6,7,8-tetrahydro-2-trifylquinazoline, 2-(2-chlorobenzoyl)imino-5-ethyl-3-[2'-(1H-tetrazole-5-yl)biphenyl-4-yl)methyl-1,3,4-thiadiazoline, 2-[5-ethyl-3-[2-(1H-tetrazole-5-yl)biphenyl-4-yl]methyl-1,3,4-thiazoline-2-ylidene]aminocarbonyl-1-cyclopentencarboxylic acid dipotassium salt, and 2-butyl-4-[N-methyl-N-(3-methylcrotonoyl)amino]-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-imidzole-5-carboxylic acid 1-ethoxycarbonyloxyethyl ester, those disclosed in patent publications EP475206, EP497150, EP539086, EP539713, EP535463, EP535465, EP542059, EP497121, EP535420, EP407342, EP415886, EP424317, EP435827, EP433983, EP475898, EP490820, EP528762, EP324377, EP323841, EP420237, EP500297, EP426021, EP480204, EP429257, EP430709, EP434249, EP446062, EP505954, EP524217, EP514197, EP514198, EP514193, EP514192, EP450566, EP468372, EP485929, EP503162, EP533058, EP467207 EP399731, EP399732, EP412848, EP453210, EP456442, EP470794, EP470795, EP495626, EP495627, EP499414, EP499416, EP499415, EP511791, EP516392, EP520723, EP520724, EP539066, EP438869, EP505893, EP530702, EP400835, EP400974, EP401030, EP407102, EP411766, EP409332, EP412594, EP419048, EP480659, EP481614, EP490587, EP467715, EP479479, EP502725, EP503838, EP505098, EP505111 EP513,979 EP507594, EP510812, EP511767, EP512675, EP512676, EP512870, EP517357, EP537937, EP534706, EP527534, EP540356, EP461040, EP540039, EP465368, EP498723, EP498722, EP498721, EP515265, EP503785, EP501892, EP519831, EP532410, EP498361, EP432737, EP504888, EP508393, EP508445, EP403159, EP403158, EP425211, EP427463, EP437103, EP481448, EP488532, EP501269, EP500409, EP540400, EP005528, EP028834, EP028833, EP411507, EP425921, EP430300, EP434038, EP442473, EP443568, EP445811, EP459136, EP483683, EP518033, EP520423, EP531876, EP531874, EP392317, EP468470, EP470543, EP502314, EP529253, EP543263,

EP540209, EP449699, EP465323, EP521768, EP415594, WO92/14468, WO93/08171, WO93/08169, WO91/00277, WO91/00281, WO91/14367, WO92/00067, WO92/00977, WO92/20342, WO93/04045, WO93/04046, WO91/15206, WO92/14714, WO92/09600, WO92/16552, WO93/05025, WO93/03018, WO91/07404, WO92/02508, WO92/13853, WO91/19697, WO91/11909, WO91/12001, WO91/11999, WO91/15209, WO91/15479, WO92/20687, WO92/20662, WO92/20661, WO93/01177, WO91/14679, WO91/13063, WO92/13564, WO91/17148, WO91/18888, WO91/19715, WO92/02257, WO92/04335, WO92/05161, WO92/07852, WO92/15577, WO93/03033, WO91/16313, WO92/00068, WO92/02510, WO92/09278, WO9210179, WO92/10180, WO92/10186, WO92/10181, WO92/10097, WO92/10183, WO92/10182, WO92/10187, WO92/10184, WO92/10188, WO92/10180, WO92/10185, WO92/20651, WO93/03722, WO93/06828, WO93/03040, WO92/19211, WO92/22533, WO92/06081, WO92/05784, WO93/00341, WO92/04343, WO92/04059, US5104877, US5187168, US5149699, US5185340, US4880804, US5138069, US4916129, US5153197, US5173494, US5137906, US5155126, US5140037, US5137902, US5157026, US5053329, US5132216, US5057522, US5066586, US5089626, US5049565, US5087702, US5124335, US5102880, US5128327, US5151435, US5202322, US5187159, US5198438, US5182288, US5036048, US5140036, US5087634, US5196537, US5153347, US5191086, US5190942, US5177097, US5212177, US5208234, US5208235, US5212195, US5130439, US5045540, US5041152, and US5210204, and pharmaceutically acceptable salts and esters thereof;

α/β adrenergic blockers such as nipradilol, arotinolol, amosulalol, bretylium tosylate (CAS RN: 61-75-6), dihydroergtamine mesylate (such as ergotaman-3', 6',18-trione,9,-10-dihydro-12'-hydroxy-2'-methyl-5'-(phenylmethyl)-,(5'(α))-, monomethanesulfonate, e.g., DHE 45® Injection, Novartis), carvedilol (such as (±)-1-(Carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol, e.g., Coreg®, SmithKline Beecham), labetalol (such as 5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl) amino] ethyl]salicylamide monohydrochloride, e.g., Normodyne®, Schering), bretylium tosylate (Benzenemethanaminium, 2-bromo-N-ethyl-N,N-dimethyl-, salt with 4-

methylbenzenesulfonic acid (1:1) CAS RN 61-75-6), phentolamine mesylate (Phenol, 3-[[(4,5-dihydro-1H-imidazol-2-yl)methyl](4-methylphenyl)amino]-, monomethanesulfonate (salt) CAS RN 65-28-1), solypertine tartrate (5H-1,3-Dioxolo[4,5-f]indole, 7-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) CAS RN 5591-43-5), zolertine hydrochloride (Piperazine, 1-phenyl4-[2-(1H-tetrazol-5-yl)ethyl]-, monohydrochloride (8Cl, 9Cl) CAS RN 7241-94-3) and the like;

α adrenergic receptor blockers, such as alfuzosin (CAS RN: 81403-68-1), terazosin, urapidil, prazosin (Minipress®), tamsulosin, bunazosin, trimazosin, doxazosin, naftopidil, indoramin, WHP 164, XEN010, fenspiride hydrochloride (which may be prepared as disclosed in US3399192), proroxan (CAS RN 33743-96-3), and labetalol hydrochloride and combinations thereof;

α 2 agonists such as methyldopa, methyldopa HCL, lofexidine, tiamenidine, moxonidine, rilmenidine, guanobenz, and the like;

aldosterone inhibitors, and the like;

angiopoietin-2-binding agents such as those disclosed in WO03/030833;

anti-angina agents such as ranolazine (hydrochloride1-Piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, dihydrochloride CAS RN 95635-56-6), betaxolol hydrochloride (2-Propanol, 1-[4-[2 (cyclopropylmethoxy)ethyl]phenoxy]-3-[(1-methylethyl)amino]-, hydrochloride CAS RN 63659-19-8), butoprozine hydrochloride (Methanone, [4-[3(dibutylamino)propoxy]phenyl](2-ethyl-3-indolizinyl)-, monohydrochloride CAS RN 62134-34-3), cinepazet maleate1-Piperazineacetic acid, 4-[1-oxo-3-(3,4,5-trimethoxyphenyl)-2-propenyl]-, ethyl ester, (2Z)-2-butenedioate (1:1) CAS RN 50679-07-7), tosifen (Benzenesulfonamide, 4-methyl-N-[[[(1S)-1-methyl-2-phenylethyl]amino]carbonyl]- CAS RN 32295-184), verapamilhydrochloride (Benzeneacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-α-(1-methylethyl)-, monohydrochloride CAS RN 152-114), molsidomine (1,2,3-Oxadiazolium, 5-[(ethoxycarbonyl)amino]-3-(4-morpholinyl)-, inner salt CAS RN 25717-80-0), and ranolazine hydrochloride (1-Piperazineacetamide, N-(2,6-dimethylphenyl)$_4$-[2-hydroxy-3-(2-meth- oxyphenoxy)propyl]-, dihydrochloride CAS

RN 95635-56-6); tosifen (Benzenesulfonamide, 4-methyl-N-[[[(1S)-1-methyl-2-phenylethyl]amino]carbonyl]- CAS RN 32295-184);

adrenergic stimulants such as guanfacine hydrochloride (such as N-amidino-2-(2,6-dichlorophenyl) acetamide hydrochloride, e.g., Tenex® Tablets available from Robins); methyldopa-hydrochlorothiazide (such as levo-3-(3,4-dihydroxyphenyl)-2-methylalanine) combined with Hydrochlorothiazide (such as 6-chloro-3,4-dihydro-2H -1,2,4-benzothiadiazine-7- sulfonamide 1,1-dioxide, e.g., the combination as, e.g., Aldoril® Tablets available from Merck), methyldopa-chlorothiazide (such as 6-chloro-2H-1, 2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and methyldopa as described above, e.g., Aldoclor®, Merck), clonidine hydrochloride (such as 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride and chlorthalidone (such as 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl) benzenesulfonamide), e.g., Combipres®, Boehringer Ingelheim), clonidine hydrochloride (such as 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride, e.g., Catapres®, Boehringer Ingelheim), clonidine (1H-Imidazol-2-amine, N-(2,6-dichlorophenyl)4,5-dihydro-CAS RN 4205-90-7); and

those agents disclosed in US20030069221. Tests showing the efficacy of the therapy and the rationale for the combination therapy with an anti-hypertensive agent are described, for example, in US20030069221.

Anti-Obesity Agents

[00120] The compounds described herein can be used in therapeutic combination with one or more anti-obesity agents, including but not limited to:

11β HSD-1 (11-beta hydroxy steroid dehydrogenase type 1) inhibitors, such as BVT 3498, BVT 2733, 3-(1-adamantyl)-4-ethyl-5-(ethylthio)- 4H-1,2,4-triazole, 3-(1-adamantyl)-5-(3,4,5-trimethoxyphenyl)-4-methyl-4H-1,2,4-triazole, 3- adamantanyl-4,5,6,7,8,9,10,11,12,3a-decahydro-1,2,4-triazolo[4,3-a][11]annulene, and those compounds disclosed in WO01/90091, WO01/90090, WO01/90092 and WO02/072084;

5HT antagonists such as those in WO03/037871, WO03/037887, and the like;

5HT1a modulators such as carbidopa, benserazide and those disclosed in US6207699,

WO03/031439, and the like;

5HT2c (serotonin receptor 2c) agonists, such as BVT933, DPCA37215, IK264, PNU 22394, WAY161503, R-1065, SB 243213 (Glaxo Smith Kline) and YM 348 and those disclosed in US3914250, WO00/77010, WO02/36596, WO02/48124, WO02/10169, WO01/66548, WO02/44152, WO02/51844, WO02/40456, and WO02/40457;

5HT6 receptor modulators, such as those in WO03/030901, WO03/035061, WO03/039547, and the like;

acyl-estrogens, such as oleoyl-estrone, disclosed in del Mar-Grasa, M. et al., Obesity Research, 9:202-9 (2001) and Japanese Patent Application No. JP 2000256190;

anorectic bicyclic compounds such as 1426 (Aventis) and 1954 (Aventis), and the compounds disclosed in WO00/18749, WO01/32638, WO01/62746, WO01/62747, and WO03/015769;

CB 1 (cannabinoid-1 receptor) antagonist/inverse agonists such as rimonabant (Acomplia; Sanofi), SR-147778 (Sanofi), SR-141716 (Sanofi), BAY 65-2520 (Bayer), and SLV 319 (Solvay), and those disclosed in patent publications US4973587, US5013837, US5081122, US5112820, US5292736, US5532237, US5624941, US6028084, US6509367, US6509367, US20060069080 (specifically including those referenced or disclosed by formulae in paragraphs 28-168), WO96/33159, WO97/29079, WO98/31227, WO98/33765, WO98/37061, WO98/41519, WO98/43635, WO98/43636, WO99/02499, WO00/10967, WO00/10968, WO01/09120, WO01/58869, WO01/64632, WO01/64633, WO01/64634, WO01/70700, WO01/96330, WO02/076949, WO03/006007, WO03/007887, WO03/020217, WO03/026647, WO03/026648, WO03/027069, WO03/027076, WO03/027114, WO03/037332, WO03/040107, WO03/086940, WO03/084943 and EP658546;

CCK-A (cholecystokinin-A) agonists, such as AR-R 15849, GI 181771 (GSK), JMV-180, A-71378, A-71623 and SR146131 (Sanofi), and those described in US5739106;

CNTF (Ciliary neurotrophic factors), such as GI-181771 (Glaxo-SmithKline), SR146131 (Sanofi Synthelabo), butabindide, PD170,292, and PD 149164 (Pfizer);

CNTF derivatives, such as Axokine® (Regeneron), and those disclosed in

WO94/09134, WO98/22128, and WO99/43813;

dipeptidyl peptidase IV (DP-IV) inhibitors, such as isoleucine thiazolidide, valine pyrrolidide, NVP-DPP728, LAF237, P93/01, P 3298, TSL 225 (tryptophyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid; disclosed by Yamada et al, Bioorg. & Med. Chem. Lett. 8 (1998) 1537-1540), TMC-2A/2B/2C, CD26 inhibtors, FE 999011, P9310/K364, VIP 0177, SDZ 274-444, 2-cyanopyrrolidides and 4-cyanopyrrolidides as disclosed by Ashworth et al, Bioorg. & Med. Chem. Lett., Vol. 6, No. 22, pp 1163-1166 and 2745-2748 (1996) and the compounds disclosed patent publications. WO99/38501, WO99/46272, WO99/67279 (Probiodrug), WO99/67278 (Probiodrug), WO99/61431 (Probiodrug), WO02/083128, WO02/062764, WO03/000180, WO03/000181, WO03/000250, WO03/002530, WO03/002531, WO03/002553, WO03/002593, WO03/004498, WO03/004496,WO03/017936, WO03/024942, WO03/024965, WO03/033524, WO03/037327 and EP1258476;

growth hormone secretagogue receptor agonists/antagonists, such as NN703, hexarelin, MK-0677 (Merck), SM-130686, CP-424391 (Pfizer), LY 444,711 (Eli Lilly), L-692,429 and L-163,255, and such as those disclosed in USSN 09/662448, US provisional application 60/203335, US6358951, US2002049196, US2002/022637, WO01/56592 and WO02/32888;

H3 (histamine H3) antagonist/inverse agonists, such as thioperamide, 3-(1H-imidazol-4-yl)propyl N-(4-pentenyl)carbamate), clobenpropit, iodophenpropit, imoproxifan, GT2394 (Gliatech), and A331440, O-[3-(1H-imidazol-4-yl)propanol]carbamates (Kiec-Kononowicz, K. et al., Pharmazie, 55:349-55 (2000)), piperidine-containing histamine H3-receptor antagonists (Lazewska, D. et al., Pharmazie, 56:927-32 (2001), benzophenone derivatives and related compounds (Sasse, A. et al., Arch. Pharm.(Weinheim) 334:45-52 (2001)), substituted N-phenylcarbamates (Reidemeister, S. et al., Pharmazie, 55:83-6 (2000)), and proxifan derivatives (Sasse, A. et al., J. Med. Chem.. 43:3335-43 (2000)) and histamine H3 receptor modulators such as those disclosed in WO02/15905, WO03/024928 and WO03/024929;

leptin derivatives, such as those disclosed in US5552524, US5552523, US5552522, US5521283, WO96/23513, WO96/23514, WO96/23515, WO96/23516, WO96/23517, WO96/23518, WO96/23519, and WO96/23520;

leptin, including recombinant human leptin (PEG-OB, Hoffman La Roche) and recombinant methionyl human leptin (Amgen);
lipase inhibitors, such as tetrahydrolipstatin (orlistat/Xenical®), Triton WR1339, RHC80267, lipstatin, teasaponin, diethylumbelliferyl phosphate, FL-386, WAY-121898, Bay-N-3176, valilactone, esteracin, ebelactone A, ebelactone B, and RHC 80267, and those disclosed in patent publications WO01/77094, US4598089, US4452813, USUS5512565, US5391571, US5602151, US4405644, US4189438, and US4242453;
lipid metabolism modulators such as maslinic acid, erythrodiol, ursolic acid uvaol, betulinic acid, betulin, and the like and compounds disclosed in WO03/011267;
Mc4r (melanocortin 4 receptor) agonists, such as CHIR86036 (Chiron), ME-10142, ME-10145, and HS-131 (Melacure), and those disclosed in PCT publication Nos. WO99/64002, WO00/74679, WO01/991752, WO01/25192, WO01/52880, WO01/74844, WO01/70708, WO01/70337, WO01/91752, WO02/059095, WO02/059107, WO02/059108, WO02/059117, WO02/06276, WO02/12166, WO02/11715, WO02/12178, WO02/15909, WO02/38544, WO02/068387, WO02/068388, WO02/067869, WO02/081430, WO03/06604, WO03/007949, WO03/009847, WO03/009850, WO03/013509, and WO03/031410;
Mc5r (melanocortin 5 receptor) modulators, such as those disclosed in WO97/19952, WO00/15826, WO00/15790, US20030092041;
melanin-concentrating hormone 1 receptor (MCHR) antagonists, such as T-226296 (Takeda), SB 568849, SNP-7941 (Synaptic), and those disclosed in patent publications WO01/21169, WO01/82925, WO01/87834, WO02/051809, WO02/06245, WO02/076929, WO02/076947, WO02/04433, WO02/51809, WO02/083134, WO02/094799, WO03/004027, WO03/13574, WO03/15769, WO03/028641, WO03/035624, WO03/033476, WO03/033480, JP13226269, and JP1437059;
mGluR5 modulators such as those disclosed in WO03/029210, WO03/047581, WO03/048137, WO03/051315, WO03/051833, WO03/053922, WO03/059904, and the like;
serotoninergic agents, such as fenfluramine (such as Pondimin® (Benzeneethanamine,

N-ethyl-alpha-methyl-3-(trifluoromethyl)-, hydrochloride), Robbins), dexfenfluramine (such as Redux® (Benzeneethanamine, N-ethyl-alpha-methyl-3-(trifluoromethyl)-, hydrochloride), Interneuron) and sibutramine ((Meridia®, Knoll/Reductil®) including racemic mixtures, as optically pure isomers (+) and (-), and pharmaceutically acceptable salts, solvents, hydrates, clathrates and prodrugs thereof including sibutramine hydrochloride monohydrate salts thereof, and those compounds disclosed in US4746680, US4806570, and US5436272, US20020006964, WO01/27068, and WO01/62341;

NE (norepinephrine) transport inhibitors, such as GW 320659, despiramine, talsupram, and nomifensine;

NPY 1 antagonists, such as BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, GI-264879A, and those disclosed in US6001836, WO96/14307, WO01/23387, WO99/51600, WO01/85690, WO01/85098, WO01/85173, and WO01/89528;

NPY5 (neuropeptide Y Y5) antagonists, such as 152,804, GW-569180A, GW-594884A, GW-587081X, GW-548118X, FR235208, FR226928, FR240662, FR252384, 1229U91, GI-264879A, CGP71683A, LY-377897, LY-366377, PD-160170, SR- 120562A, SR-120819A, JCF-104, and H409/22 and those compounds disclosed in patent publications US6140354, US6191160, US6218408, US6258837, US6313298, US6326375, US6329395, US6335345, US6337332, US6329395, US6340683, EP01010691, EP-01044970, WO97/19682, WO97/20820, WO97/20821, WO97/20822, WO97/20823, WO98/27063, WO00/107409, WO00/185714, WO00/185730, WO00/64880, WO00/68197, WO00/69849, WO/0113917, WO01/09120, WO01/14376, WO01/85714, WO01/85730, WO01/07409, WO01/02379, WO01/23388, WO01/23389, WO01/44201, WO01/62737, WO01/62738, WO01/09120, WO02/20488, WO02/22592, WO02/48152, WO02/49648, WO02/051806, WO02/094789, WO03/009845, WO03/014083, WO03/022849, WO03/028726 and Norman et al., J. Med. Chem. 43:4288-4312 (2000);

opioid antagonists, such as nalmefene (Revex®), 3-methoxynaltrexone, naloxone, and naltrexone and those disclosed in WO00/21509;

orexin antagonists, such as SB-334867-A and those disclosed in patent publications WO01/96302, WO01/68609, WO02/44172, WO02/51232, WO02/51838, WO02/089800, WO02/090355, WO03/023561, WO03/032991, and WO03/037847; PDE inhibitors (e.g., compounds which slow the degradation of cyclic AMP (cAMP) and/or cyclic GMP (cGMP) by inhibition of the phosphodiesterases, which can lead to a relative increase in the intracellular concentration of cAMP and cGMP; possible PDE inhibitors are primarily those substances which are to be numbered among the class consisting of the PDE3 inhibitors, the class consisting of the PDE4 inhibitors and/or the class consisting of the PDE5 inhibitors, in particular those substances which can be designated as mixed types of PDE3/4 inhibitors or as mixed types of PDE3/4/5 inhibitors) such as those disclosed in patent publications DE1470341, DE2108438, DE2123328, DE2305339, DE2305575, DE2315801, DE2402908, DE2413935, DE2451417, DE2459090, DE2646469, DE2727481, DE2825048, DE2837161, DE2845220, DE2847621, DE2934747, DE3021792, DE3038166, DE3044568, EP000718, EP0008408, EP0010759, EP0059948, EP0075436, EP0096517, EP0112987, EP0116948, EP0150937, EP0158380, EP0161632, EP0161918, EP0167121, EP0199127, EP0220044, EP0247725, EP0258191, EP0272910, EP0272914, EP0294647, EP0300726, EP0335386, EP0357788, EP0389282, EP0406958, EP0426180, EP0428302, EP0435811, EP0470805, EP0482208, EP0490823, EP0506194, EP0511865, EP0527117, EP0626939, EP0664289, EP0671389, EP0685474, EP0685475, EP0685479, JP92234389, JP94329652, JP95010875, US4963561, US5141931, WO9117991, WO9200968, WO9212961, WO9307146, WO9315044, WO9315045, WO9318024, WO9319068, WO9319720, WO9319747, WO9319749, WO9319751, WO9325517, WO9402465, WO9406423, WO9412461, WO9420455, WO9422852, WO9425437, WO9427947, WO9500516, WO9501980, WO9503794, WO9504045, WO9504046, WO9505386, WO9508534, WO9509623, WO9509624, WO9509627, WO9509836, WO9514667, WO9514680, WO9514681, WO9517392, WO9517399, WO9519362, WO9522520, WO9524381, WO9527692, WO9528926, WO9535281, WO9535282, WO9600218, WO9601825, WO9602541, WO9611917, DE3142982, DE1116676, DE2162096, EP0293063, EP0463756, EP0482208, EP0579496, EP0667345 US6331543,

US20050004222 (including those disclosed in formulas I-XIII and paragraphs 37-39, 85-0545 and 557-577), WO9307124, EP0163965, EP0393500, EP0510562, EP0553174, WO9501338 and WO9603399, as well as PDE5 inhibitors (such as RX-RA-69, SCH-51866, KT-734, vesnarinone, zaprinast, SKF-96231, ER-21355, BF/GP-385, NM-702 and sildenafil (Viagra®)), PDE4 inhibitors (such as RO-20-1724, MEM 1414 (R1533/R1500; Pharmacia Roche), denbufylline, rolipram, oxagrelate, nitraquazone, Y-590, DH-6471, SKF-94120, motapizone, lixazinone, indolidan, olprinone, atizoram, KS-506-G, dipamfylline, BMY-43351, atizoram, arofylline, filaminast, PDB-093, UCB-29646, CDP-840, SKF-107806, piclamilast, RS-17597, RS-25344-000, SB-207499, TIBENELAST, SB-210667, SB-211572, SB-211600, SB-212066, SB-212179, GW-3600, CDP-840, mopidamol, anagrelide, ibudilast, amrinone, pimobendan, cilostazol, quazinone and N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy4-difluoromethoxybenzamide, PDE3 inhibitors (such as sulmazole, ampizone, cilostamide, carbazeran, piroximone, imazodan, CI-930, siguazodan, adibendan, saterinone, SKF-95654, SDZ-MKS-492, 349-U-85, emoradan, EMD-53998, EMD-57033, NSP-306, NSP-307, revizinone, NM-702, WIN-62582 and WIN-63291, enoximone and milrinone, PDE3/4 inhibitors (such as benafentrine, trequinsin, ORG-30029, zardaverine, L-686398, SDZ-ISQ-844, ORG-20241, EMD-54622, and tolafentrine) and other PDE inhibitors (such as cilomilast, fenoximone, pentoxifylline, roflumilast, tadalafil(Cialis®), theophylline, and vardenafil(Levitra®); Neuropeptide Y2 (NPY2) agonists include but are not limited to: peptide YY and fragments and variants thereof (e.g., YY3–36 (PYY3-36) (N. Engl. J. Med. 349:941, 2003; CAS RN. 870491-48-8) and PYY agonists such as those disclosed in WO03/026591, WO03/057235, and WO03/027637;

serotonin reuptake inhibitors, such as, paroxetine, fluoxetine (Prozac®), fluvoxamine, sertraline, citalopram, and imipramine, and those disclosed in US6162805, US6365633, WO03/00663, WO01/27060, and WO01/162341;

thyroid hormone β agonists, such as QRX-431 (QuatRx), GC-24 (described in US 20040110154), KB-2611 (KaroBioBMS), and those disclosed in WO02/15845, WO97/21993, WO99/00353, GB98/284425, U.S. Provisional Application No. 60/183,223, and Japanese Patent Application No. JP 2000256190;

UCP-1 (uncoupling protein-1), 2, or 3 activators, such as phytanic acid, 4-[(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-napthalenyl)-1-propenyl]benzoic acid (TTNPB), retinoic acid, and those disclosed in WO99/00123;
β3 (beta adrenergic receptor 3) agonists, such as AJ9677/TAK677 (Dainippon/Takeda), L750355 (Merck), CP331648 (Pfizer), CL-316,243, SB 418790, BRL-37344, L-796568, BMS-196085, BRL-35135A, CGP12177A, BTA-243, GW 427353, Trecadrine, Zeneca D7114, N-5984 (Nisshin Kyorin), LY-377604 (Lilly), SR 59119A, and those disclosed in US5541204, US5770615, US5491134, US5776983, US488064, US5705515, US5451677, WO94/18161, WO95/29159, WO97/46556, WO98/04526 and WO98/32753, WO01/74782, WO02/32897, WO03/014113, WO03/016276, WO03/016307, WO03/024948, WO03/024953 and WO03/037881;
noradrenergic agents including, but not limited to, diethylpropion (such as Tenuate® (1-propanone, 2-(diethylamino)-1-phenyl-, hydrochloride), Merrell), dextroamphetamine (also known as dextroamphetamine sulfate, dexamphetamine, dexedrine, Dexampex, Ferndex, Oxydess II, Robese, Spancap #1), mazindol ((or 5-(p-chlorophenyl)-2,5-dihydro-3H-imidazo[2,1-a]isoindol-5-ol) such as Sanorex®, Novartis or Mazanor®, Wyeth Ayerst), phenylpropanolamine (or Benzenemethanol, alpha-(1-aminoethyl)-, hydrochloride), phentermine ((or Phenol, 3-[[4,5-duhydro-1H-imidazol-2-yl)ethyl](4-methylpheny-l)amino], monohydrochloride) such as Adipex-P®, Lemmon, FASTIN®, Smith-Kline Beecham and Ionamin®, Medeva), phendimetrazine ((or (2S,3S)-3,4-Dimethyl-2phenylmorpholine L-(+)-tartrate (1:1)) such as Metra® (Forest) , Plegine® (Wyeth-Ayerst), Prelu-2® (Boehringer Ingelheim), and Statobex® (Lemmon), phendamine tartrate (such as Thephorin® (2,3,4,9-Tetrahydro-2-methyl-9-phenyl-1H-indenol[2,1-c]pyridine L-(+)-tartrate (1:1)), Hoffmann-LaRoche), methamphetamine (such as Desoxyn®, Abbot ((S)--N, (alpha)-dimethylbenzeneethanamine hydrochloride)), and phendimetrazine tartrate (such as Bontril® Slow-Release Capsules, Amarin (-3,4-Dimethyl-2-phenylmorpholine Tartrate);
fatty acid oxidation upregulator/inducers such as Famoxin® (Genset);
monamine oxidase inhibitors including but not limited to befloxatone, moclobemide, brofaromine, phenoxathine, esuprone, befol, toloxatone, pirlindol, amiflamine,

sercloremine, bazinaprine, lazabemide, milacemide, caroxazone and other certain compounds as disclosed by WO01/12176; and

other anti-obesity agents such as 5HT-2 agonists, ACC (acetyl-CoA carboxylase) inhibitors such as those described in WO03/072197, alpha-lipoic acid (alpha-LA), AOD9604, appetite suppressants such as those in WO03/40107, ATL-962 (Alizyme PLC), benzocaine, benzphetamine hydrochloride (Didrex), bladderwrack (focus vesiculosus), BRS3 (bombesin receptor subtype 3) agonists, bupropion, caffeine, CCK agonists, chitosan, chromium, conjugated linoleic acid, corticotropin-releasing hormone agonists, dehydroepiandrosterone, DGAT1 (diacylglycerol acyltransferase 1) inhibitors, DGAT2 (diacylglycerol acyltransferase 2) inhibitors, dicarboxylate transporter inhibitors, ephedra, exendin-4 (an inhibitor of glp-1) FAS (fatty acid synthase) inhibitors (such as Cerulenin and C75), fat resorption inhibitors (such as those in WO03/053451, and the like), fatty acid transporter inhibitors, natural water soluble fibers (such as psyllium, plantago, guar, oat, pectin), galanin antagonists, galega (Goat's Rue, French Lilac), garcinia cambogia, germander (teucrium chamaedrys), ghrelin antibodies and ghrelin antagonists (such as those disclosed in WO01/87335, and WO02/08250), GLP-1 (glucagon-like peptide 1) agonists (e.g., exendin-4), glp-1 (glucagon-like peptide-1), glucocorticoid antagonists, glucose transporter inhibitors, growth hormone secretagogues (such as those disclosed and specifically described in US5536716), interleukin-6 (IL-6) and modulators thereof (as in WO03/057237, and the like), L-carnitine, Mc3r (melanocortin 3 receptor) agonists, MCH2R (melanin concentrating hormone 2R) agonist/antagonists, melanin concentrating hormone antagonists, melanocortin agonists (such as Melanotan II or those described in WO 99/64002 and WO 00/74679), nomame herba, phosphate transporter inhibitors, phytopharm compound 57 (CP 644,673), pyruvate, SCD-1 (stearoyl-CoA desaturase-1) inhibitors, T71 (Tularik, Inc., Boulder CO), Topiramate (Topimax®, indicated as an anti-convulsant which has been shown to increase weight loss), transcription factor modulators (such as those disclosed in WO03/026576), β-hydroxy steroid dehydrogenase-1 inhibitors (β -HSD-1), β-hydroxy-β-methylbutyrate, p57 (Pfizer), Zonisamide (Zonegran®, indicated as an anti-epileptic which has been shown to lead to weight loss), and the agents disclosed in US20030119428 paragraphs

20-26. Tests showing the efficacy of the therapy and the rationale for the combination therapy with an anti-obesity agent are presented in US20030119428.

Agents used to treat autoimmune disorders

[00121] The compounds described herein can be used in therapeutic combination with one or more agents used to treat autoimmune disorders including, but not limited to: (a) disease modifying antirheumatic drugs, including methotrexate, gold salts, D-penicillamine, hydroxychloroquine, auranofin, sulfsalazine; (b) nonsteroidal anitinflammatory drugs, including indomethacin, naproxen, diclofenac, ibuprofen, aspirin and aspirin analogs, acetaminophen; (c) COX-2 selective inhibitors, including celecoxib, rofecoxib, etoricoxib, valdecoxib, lumiracoxib; (d) COX-1 inhibitors; (e) immunosuppressives, including calcineurin inhibitors such as cyclosporine and FK506; $p70^{S6}$ kinase inhibitors such as sirolimus and rapamycin; inosine monophosphate dehydrogenase inhibitors such as mycophenolate (including mycophenolate mofetil); leflunomide, cyclophosphamide, azathioprine; (f) steroids, including prednisone, betamethasone, budesonide and dexamethasone; (g) biological response modifiers, including TNFα antagonists such as infliximab, adalimmab and etanercept; IL-1 receptor antagonists such as anakinra; humanized or chimeric antibodies or fusion proteins such as alefacept, efalizumab, daclizumab; anti-chemokine antibodies or interleukins; and (h) other agents useful for the treatment of autoimmune disorders, including chemokine receptor antagonists or modulators, cannabinoid receptor antagonists or modulators, inhibitors of matrix metalloproteinases including those described herein, TNFα-converting enzymes, nitric oxide synthetases or phosphodiesterase IV, such as roflumilast or cilomilast; inhibitors of p38 MAP-kinase, the NF-kappa.beta., pathway or IL-1 receptor associated kinase or inhibitors of interactions involving adhesion molecules such as LFA-1, VLA-4, ICAM-1, VCAM-1, $\alpha_4\beta_7$, MAdCAM-1, and $\alpha_v\beta_3$. Tests showing the efficacy of the therapy and the rationale for the combination therapy with agents used to treat autoimmune disorders are presented in US20040092499.

Agents used to treat demylenation and associated conditions

[00122] The compounds described herein can be used in therapeutic combination with one or more agents used to treat demylenation and its associated conditions including, but not limited to: beta-interferon (such as Avonex®, Biogen, Inc. and Betaseron®, Berlex Laboratories), which can decrease the frequency and occurrence of flare-ups and slow the progression to disability, glatiramer acetate (such as Copaxone®, Teva Neuroscience, Inc.), which can reduce the frequency of relapses, and/or administration of corticosteroids, such as prednisone (available from Roxane), to relieve acute symptoms. The amount of respective antidemyelination agent to be administered to the subject readily can be determined by one skilled in the art from the Physician's Desk Reference (56.sup.th Ed. 2002) at pages 1013-1016, 988995, 3306-3310 and 3064-3066, incorporated herein by reference. Tests showing the efficacy of the therapy and the rationale for the combination therapy with agents used to treat demylenation and its associated conditions are described, for example, in US20040092500.

Agents used to treat Alzheimer's disease

[00123] The compounds described herein can be used in therapeutic combination with one or more agents used to treat Alzheimer's disease including, but not limited to: cholinesterase inhibitors (such as donepezil hydrochloride (such as Aricept® (Pfizer)), rivastigmine tartrate (such as Exelon (Novartis)), tacrine (such as Cognex® (Parke-Davis)), galanthamine and derivatives thereof (Janssen), metrifonate (Bayer Corp.), epigalanthamine, norgalanthamine, fasciculin, metrifonate, heptyl-physostigmine, norpyridostigmine, nomeostigmine, ipidacrine (Nikken Chemicals Co. Ltd.), TAK-147 & T-82 (SS Pharmaceutical Co. Ltd.), methanesulfonyl fluoride, CHF-2819, phenserine, physostigmine (Forest Laboratories, Inc.), huperzine, cymserine (Anonyx Inc.), tolserine (National Institutes of Health), ER-127528 (Eisai Co. Ltd.), and combinations thereof), muscarinic receptor agonists (such as aceclide, pilocarpine, oxotremorine, arecaidine, 5-methylfurmethiodide, cevimeline, PD-151832 (Pfizer Inc.), YM-796 (Yamanouchi Pharmaceutical Inc.), P-58 (Phytopharm

plc) and combinations thereof), M2 muscarinic receptor antagonists, acetylcholine release stimulators (such as minaprine, montirelin (Grunenthal GmbH), T-588 (Toyama Chemical Co. Ltd.), XE-991 and combinations thereof, choline uptake stimulators (such as MKC-231 (Mitsubishi-Tokyo Pharmaceuticals Inc)), nicotinic cholinergic receptor agonists (such as altinicline, (SIBIA Neurosciences Inc.), SIB-1553A, ABT-089 (disclosed in US5278176, Abbot), nicotine patch, GRS-21, TC-2403 and combinations thereof), anti-Aβ vaccines (such as AN-1792), γ-secretase inhibitors or β-secretase inhibitors (such as Asn^{670},Sta^{671},Val^{672}-Amyloid β/A4 Protein $Precursor_{770}$ (662-675) (catalog no. H-4948; Bachem), presenilin-1, presenilin-2 and derivatives thereof comprising one or more conservative substitutions), amyloid aggregation inhibitors (such as reumacon (Conpharm AB), NC-531 (Neurochem Inc.), PPI-1019 (Praecis Pharmaceuticals Inc.) and combinations thereof), amyloid precursor protein antisense oligonucleotides, monoamine reuptake inhibitors (such as NS-2330), human stem cells, gene therapy, nootropic agents (such as oxiracetam (ISF Societa Per Azioni), pramiracetam (Warner Lambert), idebenone (Takeda Chemical Inds. Ltd.), anapsos (ASAC Pharmaceuticals Intl.), nebracetam (Boehringer Ingelheim), JTP-2942 (Japan Tobacco Inc.), fasoracetam (Nippon Shinyaku Co. Ltd.), bacosides (Central Drug Research Institute), alzene (Bar-Ilan University), KA-672 (Dr. Willmar Schwabe GmbH & Co.), alaptid (VUFB), IQ-200, ALE-26015 (Allelix Pharm-Eco LP) and combinations thereof), AMPA receptor ligands (such as CX-516 & CX-691 (Cortex Pharmaceuticals Inc.) and combinations thereof), growth factors or growth factor receptor agonists (such as leteprinim), anti-inflammatory agents (such as COX2 inhibitors (such as Vioxx rofecoxib (Merck) and Celebrex celecoxib (Pfizer), cytokine inhibitors (such as thalidomide disclosed in WO95/04533 and dexanabinol), complement inhibitors, leukotriene receptor antagonists and combinations thereof, free radical scavengers (such as EGb-761 (Yuyu Industrial Co.), CPI-22, dexanabinol and combinations thereof), antioxidants, superoxide dismutase stimulators, calcium channel blockers (such as tamolarizine (Nippon Chemiphar Co., Ltd.), nimodipine (Bayer AG), PD-1 76078 (Elan Pharmaceuticals, Inc.), and combinations thereof), apoptosis inhibitors (such as acetyl-L-carnitine, CEP-1347 (Cephalon, Inc.), TCH-346 (Novartis AG) and combinations thereof), caspase inhibitors (such as pralnacasan),

monoamine oxidase inhibitors (such as moclobemide (Roche Holding AG), selegiline, rasagiline (Teva Pharmaceutical Inds. Ltd.), SL-25.1188, Ro-41-1049 (Roche Holding AG), and combinations thereof), estrogens and estrogen receptor ligands, NMDA receptor antagonists (such as ketamine, phencyclidine, dizocilpine, tiletamine, dextromethorphan, amantadine, methadone, dextropropoxyphene, ketobemidone, memantine, ipenoxazone (Nippon Chemiphar Co. Ltd. and combinations thereof), Jun N-terminal kinase (JNK) inhibitors, copper/zinc chelators (such as clioquinol (PN Gerolymatos SA)), 5-HT1a receptor agonists (such as AP-159 (Asahi Kasei Corp)), NGF stimulators (such as xaliprodene (Sanofi-Synthelabo)), neuroprotective agents (such as citicholine, GS-1590 (Leo Pharmaceutical Products Ltd.) A/S, CPI-1189 (Centaur Pharmaceuticals Inc.), SR-57667 (Sanofi-Synthelabo) and combinations thereof), H_3 histamine receptor antagonists (such as GT-2016 and GT-2331 (both available from Gliatech, Inc.) and combinations thereof), calpain inhibitors, poly ADP ribose polymerase inhibitors, prolylendopeptidase inhibitors (such as ONO-1603 (Ono Pharmaceutical Co. Ltd.), Z-321 (Zeria Pharmaceutical Co. Ltd.) and combinations thereof), calcium modulators (such as neurocalc (Apollo Biopharmaceuticals Inc)), corticortropin releasing factor receptor antagonists (such as NBI-113 (Neurocrine Biosciences, Inc)), corticortropin releasing factor binding protein inhibitors, GABA modulators (such as NGD 97-1 (Neurogen Corp)), GABA-A receptor antagonists, GABA-B receptor antagonists, neuroimmunophilin ligands, sigma receptor ligands (such as igmesine (Pfizer)), galanin receptor ligands, imidazoline/alpha adrenergic receptor antagonists (such as efaroxan (Reckitt & Colman PLC)), vasoactive intestinal peptide receptor agonists (such as stearyl-NIe-VIP), benzodiazepine receptor inverse agonists (such as S-8510 (Shionogi & Co. Ltd)), cannabinoid receptor agonists (such as dronabinol (Unimed Pharmaceuticals Inc)), thyrotropin releasing hormone receptor agonists (such as taltireline (Tanabe Seiyaku Co. Ltd) and protirelin (Takeda Chemical Inds., Inc.)), protein kinase C inhibitors, 5-HT3 receptor antagonists (such as GYKI-46903), prostaglandin receptor antagonists, topoisomerase II inhibitors (such as iododoxorubicin (Pharmacia & Upjohn AB)), steroid receptor ligand (such as GL-701 (Prestara)), nitric oxide modulators, RAGE inhibitors (such as ALT-711 (Alteon Inc)), dopamine receptor agonists (such as speramine), statine compounds disclosed in

US20050090449, corticosteroid receptor antagonist (such as anticort) and combinations thereof. Tests showing the efficacy of the therapy and the rationale for the combination therapy with agents used to treat Alzheimer's disease and other memory associated therapies are described, for example, in US2003013699 and US 20040044023.

Blood Modifiers

[00124] The compounds described herein can be used in therapeutic combination with one or more blood modifiers, i.e., agents capable of altering the number of platelets per a given volume of blood, inhibiting platelet function, including but not limited to platelet adhesion, aggregation or factor release, or reducing platelet count in patients with abnormally high levels in certain hematological malignancies to levels approximating normal levels capable of impacting negatively upon the formation of blood clots, and decreasing blood viscosity. Blood modifiers useful in the present invention include but are not limited to anti-coagulants, antithrombotic agents, fibrinogen receptor antagonists, platelet inhibitors, platelet aggregation inhibitors, lipoprotein-associated coagulation inhibitor, hemorrheologic agents, Factor VIIa inhibitors, Factor Xa inhibitors, and combinations thereof. Tests showing the efficacy of the therapy and the rationale for the combination therapy with blood modifiers are described, for example, in US20020147184.

[00125] Anti-coagulant agents are agents which inhibit the coagulation pathway by impacting negatively upon the production, deposition, cleavage and/or activation of factors essential in the formation of a blood clot. Useful anti-coagulant agents include but are not limited to argatroban (2-Piperidinecarboxylic acid, 1-[(2S)-5-[(aminoiminomethyl)amino]-1-oxo-2-[[(1,2,3,4-tetrahydro-3-methyl-8-quinolinyl)sulfonyl]amino]pentyl]4-methyl-, CAS RN 74863-84-6), bivalirudin (CAS RN 128270-60-0), dalteparin sodium (heparin) e.g., Fragmin® Injection (Pharmacia & Upjohn), desirudin (Hirudin (Hirudo medicinalis isoform HV1), 63-desulfo CAS RN 120993-53-5), dicumarol (2H-1-Benzopyran-2-one, 3,3'-methylenebis[4-hydroxy-CAS RN 66-76-2 e.g., Mebaral® (Sanofi-Synthelabo)), lyapolate sodium (Ethenesulfonic acid, homopolymer, sodium salt CAS RN 25053-274), nafamostate

mesylate (Benzoic acid, 4-[(aminoiminomethyl)amino]-, 6-(aminoiminomethyl)-2-naphthalenyl ester, dimethanesulfonate CAS RN 82956-11-4);phenprocoumon (2H-1-Benzopyran-2-one, 4-hydroxy-8-methoxy-3-(- 1-phenylpropyl)-CAS RN 132605-68-6), tinzaparin sodium (Heparin, sodium salt, CAS RN 9041-08-1, e.g., Innohep® Injection® (DuPont)), and warfarin sodium (3-((alpha)-acetonylbenzyl)-4-hydroxycoumarin, CAS RN 129-06-6, e.g., Coumadin for Injection (DuPont)).

[00126] Anti-thrombotic agents are agents which prevent the formation of a blood thrombus. A thrombus is an aggregation of blood factors, primarily platelets and fibrin with entrapment of cellular elements, frequently causing vascular obstruction at the point of its formation. Suitable examples of anti-thrombotic agents include, but are not limited to: melagatran; ximelagatran (Exanta®); anagrelide hydrochloride (6,7-dichloro-1,5-dihydroimidazo[2,1-b]quinazolin-2(3H)-one monohydrochloride monohydrate) e.g., Agrylin® (Shire US)); Tinzaparin sodium as described above; cilostazol (6-[4-(1-cyclohexyl-1H -tetrazol-5-yl)butoxy]-3,4-dihydro-2(1 H)-quinolinone, CAS-73963-72-1, e.g., Pletal® (Pharmacia & Upjohn); Dalteparin sodium (as described above); danaparoid sodium, e.g., Orgaran® Injection (Organon); compounds disclosed in WO99/45913; Abciximab is the (Fab fragment of the chimeric human-murine monoclonal antibody 7E3. binds to the glycoprotein (GP) IIb/IIIa $((\alpha)_{IIb}\ (\beta)_3)$ receptor of human platelets and inhibits platelet aggregation. Abciximab also binds to the vitronectin $((\alpha)_V\ (\beta)_3)$ receptor found on platelets and vessel wall endothelial and smooth muscle cells, e.g., Abciximab, Reopro® (Lily)); ifetroban (Benzenepropanoic acid, 2-[[(1S,2R,3S,4R)-3-[4-[(pentylamino)carbonyl]-2-oxazolyl]-7 oxabicyclo[2.2.1]hept-2-yl]methyl]-CAS RN 143443-90-7, disclosed in US5100889); Bivalirudin as described above; Cilostazol as described above; efegatran sulfate (L-Prolinamide, N-methyl-D-phenylalanyl-N-[(1S)- 4-[(aminoiminomethyl)amino]-1-formylbutyl]-, sulfate (1:1) CAS RN 126721-07-1); dazoxiben hydrochloride (Benzoic acid, 4-[2-(1H-imidazol-1-yl)ethoxy]-, monohydrochloride CAS RN 74226-22-5); danaparoid sodium (a low molecular weight heparinoid, a mixture of the sodium salts of heparan sulfate (approximately 84%), dermatan sulfate (approximately 12%), and chondroitin sulfate (approximately 4%). It is derived from hog intestinal mucosa); lotrafiban hydrochloride (1H-1,4-

Benzodiazepine-2-acetic acid, 7-([4,4'-bipiperidin]-1-ylcarbonyl)-2,3,4,5-tetrahydro4-methyl-3-oxo-, monohydrochloride, (2S)-)CAS RN 179599-82-7); ifetroban sodium(Benzenepropanoic acid, 2-[[(1S,2R,3S,4R)-3-[4-[(pentylamino)carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]-, monosodium salt, CAS RN 156715-37-6); lamifiban(Acetic acid, [[1-[(2S)-2-[[4-(aminoiminomethyl)benzoyl]amino]-3-(4-hydroxyphenyl)-1-oxopropyl]-4-piperidinyl]oxy]-, CAS RN 144412-49-7); fluretofen (1,1'-Biphenyl, 4'-ethynyl-2-fluoro-CAS RN 56917-294); enoxaparin sodium (Heparin, sodium salt, CAS RN 9041-08-1); orbofiban acetate hydrate (beta.-Alanine, N-[[[(3S)-1-[4-(aminoiminomethyl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-, ethyl ester, acetate, hydrate (4:4:1), CAS RN 165800-05-5));napsagatran (Glycine, N-[[(3S)-1-(aminoiminomethyl)-3-piperidinyl]methyl]-N2-(2-naphthalenylsul- fonyl)-L-asparaginyl-N-cyclopropyl-, CAS RN 154397-77-0); roxifiban acetate(L-Alanine, 3-[[[(5R)-3-[4-(aminoiminomethyl)phenyl]-4,5-dihydro-5-isoxazolyl]acetyl]amino]-N-(butoxycarbonyl)-, methyl ester, monoacetate, CAS RN 176022-59-6); sibrafiban(Acetic acid, [[1-[(2S)-2-[[4-[(Z)-amino(hydroxyimino)methyl]benzoyl]amino]-1-oxopropyl]4-piperidinyl]oxy]-, ethyl ester, CAS RN 172927-65-0); zolimomab aritox, (Immunoglobulin G1, anti-(human CD5 (antigen) heavy chain) (mouse monoclonal H65-RTA .gamma.1-chain), disulfide with mouse monoclonal H65-RTA light chain, dimer, disulfide with ricin (castor bean A-chain), CAS RN 141483-72-9); trifenagrel (Ethanamine, 2-[2-(4,5-diphenyl-1H-imidazol-2-yl)phenoxyl-N,N- -dimethyl-, CAS RN 84203-09-8).

[00127] Fibrinogen receptor antagonists are those agents which inhibit the common pathway of platelet aggregation. Suitable fibrinogen receptor antagonists include but are not limited toroxifiban acetate as described above; lotrafiban hydrochloride as described above, sibrafiban as described above, monoclonal antibody 7E3 (Fab fragment of the chimeric human-murine monoclonal antibody 7E3. binds to the glycoprotein (GP) IIb/IIIa $((\alpha)_{IIb}\ (\beta)_3)$ receptor of human platelets and inhibits platelet aggregation); orbofiban, (beta.-Alanine, N-[[[(3S)-1-[4-(aminoiminomethyl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-, ethyl ester, CAS RN 163250-90-6); xemilofiban (4-Pentynoic acid, 3-[[4-[[4-(aminoiminomethyl)phenyl]amino]-1,4-dioxobutyl]amino]-, ethyl ester, (3S)-,CAS RN 149820-74-6); fradafiban, (3-

Pyrrolidineacetic acid, 5-[[[4'-(aminoiminomethyl)[1,1'-biphenyl]-4-yl]oxy]methyl]-2-oxo-, (3S,5S)-,CAS RN 148396-36-5); tirofiban (L-Tyrosine, N-(butylsulfonyl)-O-[4-(4-piperidinyl)butyl]-, CAS RN 144494-65-5, e.g., Aggrastat® Injection Premixed (Merck).

[00128] Platelet inhibitors are those agents that impair the ability of mature platelets to perform their normal physiological roles (i.e., their normal function). Platelets are normally involved in a number of physiological processes such as adhesion, for example, to cellular and non-cellular entities, aggregation, for example, for the purpose of forming a blood clot, and release of factors such as growth factors (e.g., platelet-derived growth factor (PDGF)) and platelet granular components. Suitable platelet inhibitors include, but are not limited to CS-747 (Eli Lilly); eptifibatide (Integrilin®); clopidogrel bisulfate, (Thieno[3,2-c]pyridine-5(4H)-acetic acid, α-(2-chlorophenyl)-6,7-dihydro-, methyl ester, (αS)-, sulfate (1:1), e.g., Plavix® (Sanofi-Synthelabo)); indomethacin, such as Indocin® I.V. (Indomethacin Sodium Trihydrate, Merck);mefenamate, (e.g., Ponstel® Kapseals (mefenamic acid) 2-{(2,3-dimethylphenyl)amino-N-2,3- -xylylanthranilic acid (First Horizan)); Ticlopidine hydrochloride, (Thieno[3,2-c]pyridine, 5-[(2-chlorophenyl)methyl]-4,5,6,7-tetrahydro-, hydrochloride, e.g., Ticlid® (Roche Laboratories)); epoprostenol sodium, (Prosta-5,13-dien-1-oic acid, 6,9-epoxy-11,15-dihydroxy-, monosodium salt, (5Z,9α,11α,13E,15S)-CAS RN 61849-14-7, e.g., Flolan® (Glaxo Wellcome)); aspirin, Benzoic acid, 2-(acetyloxy)-CAS RN 50-78-2); epoprostenol, (Prosta-5,13-dien-1-oic acid, 6,9-epoxy-11,15-dihydroxy-, (5Z,9α,11α,13E,15S)-, CAS RN 35121-78-9); naproxen (2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, (αS)-CAS RN 22204-53-1, e.g., EC-Naprosyn® Delayed-Release Tablets available from Roche Laboratories); buprofen, (Benzeneacetic acid, α-methyl-4-(2-methylpropyl)-, CAS RN 15687-27-1); droxicam, (2H,5H-1,3-Oxazino[5,6-c][1,2]benzothiazine-2,4(3H)-dione, 5-methyl-3-(2-pyridinyl)-, 6,6-dioxide, CAS RN 90101-16-9); diclofenac, (Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-CAS RN 15307-86-5 e.g., Arthroteo® (Searle)); sulfinpyrazone, (3,5-Pyrazolidinedione, 1,2-diphenyl-4-[2-(phenylsulfinyl)ethyl]-CAS RN 57-96-5, e.g., Sectral® (Wyeth-Ayerst)); piroxicam, (2H-1,2-Benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-N-2-pyridinyl-, 1,1-dioxide, CAS RN 36322-90-4,

e.g., Feldene® (Pfizer)); dipyridamole, (Ethanol, 2,2',2",2'"-[(4,8-di-1-piperidinylpyrimido[5,4-d]- pyrimidine-2,6-diyl)dinitrilo]tetrakis-CAS RN 58-32-2, e.g., Aggrenox® Capsules available from Boehringer Ingelheim); lexipafant,(L-Leucine, N-methyl-N-[[4-[(2-methyl-1H-imidazo[4,5-c]pyridin-1-yl)methyl]phenyl]sulfonyl]-, ethyl ester, CAS RN 139133-26-9); apafant Morpholine, 4-[3-[4-(2-chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-2-yl]-1-oxopropyl]-, CAS RN 105219-56-5).

[00129] Platelet aggregation inhibitors as used herein refer to those compounds which reduce or halt the ability of platelets to associate physically with themselves or with other cellular and non-cellular components, thereby precluding the ability of a platelet to form a thrombus. Suitable platelet aggregation inhibitors include but are not limited to beraprost, (1H-Cyclopenta[b]benzofuran-5-butanoic acid, 2,3,3a,8b-tetrahydro-2-hydroxy-1-(3-hydroxy4-methyl-1-octen-6-ynyl)-, CAS RN 88430-50-6); acadesine, (1H-Imidazole-4-carboxamide, 5-amino-1β-D-ribofuranosyl-, CAS RN 2627-69-2);beraprost sodium, (1H-Cyclopenta[b]benzofuran-5-butanoic acid, 2,3,3a,8b-tetrahydro-2-hydroxy-1-(3-hydroxy4-methyl-1-octen-6-ynyl)-, monosodium salt, CAS RN 88475-69-8); ciprostene calcium, (Pentanoic acid, 5-[(3aS,5R,6R,6aR)-hexahydro-5-hydroxy-6-[(1E,3S)-3-hydroxy-1-octenyl]-3a-methyl-2(1H)-pentalenylidene]-, calcium salt (2:1), (5Z)-CAS RN 81703-55-1), Itazigrel, (Thiazole, 4,5-bis(4-methoxyphenyl)-2-(trifluoromethyl)-CAS RN 70529-35-0); lifarizine(Piperazine, 1-(diphenylmethyl)-4-[[5-methyl-2-(4-methylphenyl)-1H-imidazol-4-yl]methy- 1]-),CAS RN 119514-66-8);oxagrelate, (6-Phthalazinecarboxylic acid, 3,4-dihydro-1-(hydroxymethyl)-5,7-dimethyl-4-oxo-, ethyl ester, CAS RN 56611-65-5).

[00130] Hemorrheologic agent as used herein describes those compounds which improve the flow properties of blood by decreasing its viscosity. A suitable hemorrheologic agent of the present invention is pentoxifylline (1H-Purine-2,6-dione, 3,7-dihydro-3,7-dimethyl-1-(5-oxohexyl)-(9Cl) (CA INDEX NAME) Theobromine, 1-(5-oxohexyl)- ,CAS RN 6493-05-6 e.g., Trentali® (Aventis)).

[00131] Pentoxifylline and its metabolites (which can be useful in the present invention) improve the flow properties of blood by decreasing its viscosity. In patients

with chronic peripheral arterial disease, this increases blood flow to the affected microcirculation and enhances tissue oxygenation. The precise mode of action of pentoxifylline and the sequence of events leading to clinical improvement are still to be defined. Pentoxifylline administration has been shown to produce dose-related hemorrheologic effects, lowering blood viscosity, and improving erythrocyte flexibility. Leukocyte properties of hemorrheologic importance have been modified in animal and in vitro human studies. Pentoxifylline has been shown to increase leukocyte deformability and to inhibit neutrophil adhesion and activation. Tissue oxygen levels have been shown to be significantly increased by therapeutic doses of pentoxifylline in patients with peripheral arterial disease.

[00132] Lipoprotein-associated coagulation inhibitor (LACI) is a serum glycoprotein with a molecular weight of 38,000 Kd useful as a blood modifier of the present invention It is also known as tissue factor inhibitor because it is a natural inhibitor of thromboplastin (tissue factor) induced coagulation (US5110730 and US5106833 described tissue factor and are hereby incorporated by reference their entireties). LACI is a protease inhibitor and has 3 Kunitz domains, two of which are known to interact with factors VII and Xa respectively, while the function of the third domain is unknown. Many of the structural features of LACI can be deduced because of its homology with other well studies proteases. LACI is not an enzyme, so it probably inhibits its protease target in a stoichiometric manner; namely, one of the domains of LACI inhibits one protease molecule (see US606374).

[00133] Factor VIIa Inhibitors as used herein are those agents which inhibit activated Factor VIIa from acting to contribute to the formation of a fibrin clot. Suitable Factor VIIa Inhibitors include but are not limited to, 4H-31-benzoxazin-4-ones, 4H-3,1-benzoxazin-4-thiones, quinazolin-4-thiones, benzothiazin-4-ones described in US6180625, imidazolyl-boronic acid-derived peptide analogues as described in US5639739, TFPI-derived peptides described in US6180625.

[00134] Additional suitable Factor VIIa Inhibitors include but are not limited to Naphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)-benzyl]-2-oxo-pyrrolidin-3-(S)-yl}amide trifluoroacetate, dibenzofuran-2-sulfoic acid {1-[3-(aminomethyl)-benzyl]-5-oxo-pyrrolidin-3-yl}-amide, tolulene-4-sulfonic acid {1-[3-

(aminoiminomethyl)-benzyl]-2-oxo-pyrrolidin-3-(S)-yl}-amide tribluoroacetate, 3,4-dihydro- 1H-isoquinoline-2-sulfonic acid {1-[3-(aminoiminomethyl)-benzyl]-2-oxo-pyrrolin-3-(S)-yl}-amide tribluoroacetate or combinations thereof.

[00135] Factor Xa inhibitors as used herein are those agents which inhibit activated Factor X from acting to contribute to the formation of a fibrin clot. Suitable agents for use in the present invention as Factor Xa inhibitors include but are not limited to disubstituted pyrazolines, disubstituted triazolines as described in US6191159, lipoprotein-associated coagulation inhibitor (LACI) (as described above), low molecular weight heparins described as below, heparinoids described as below, benzimidazolines, benzoxazolinones, bensopiperazinones, indanones, as described in U.S. Pat. No. 6,207,697, dibasic (amidinoaryl)propanoic acid derivatives as described in J. Med. Chem. 37:1200-1207 (1994), bis-arlysulfonylaminobenzamide derivatives as described in US5612378, amidinophenyl-pyrrolidines, amidinophenyl-pyrrolines, amidinophenyl-isoxazolidines as described in US6057342, amidinoindoles, amidinoazoles as described in US6043257, peptidic Factor Xa inhibitors as described below, substituted n-[(aminoiminomethyl)phenyl]propylamides, substituted n-[(aminomethyl)phenyl]propylamides as described in US6080767 or combinations thereof.

[00136] Peptidic factor Xa inhibitors such as the leech-derived, 119-amino acid protein antistasin and the soft tick derived protein TAP (tick anticoagulant peptide) accelerate clot lysis and prevented reocclusion when given as adjuncts to thrombolysis (Melloff et al., Circulation Research 70:1152-1160 (1992); Sitko et al., Circulation 85:805-815 (1992)). U.S. Pat. No. 5,385,885 issued Jan. 31, 1995 discloses smooth muscle cell proliferation inhibitory activity of both tick anticoagulant peptide and antistasin. The peptide ecotin is another selective, reversible, tight-binding inhibitor of factor Xa that exhibits protein anticoagulant activity (Seymour et al., Biochemistry 33:3949-3959 (1994); WO94/20535, Sep. 14, 1994). Ixodidae, argasin and ancylostomatin are other representative peptidic factor Xa inhibitors isolated from animals that feed on blood (Markwardt, Thrombosis and Hemostasis 72: 477-479 (1994).

[00137] These non-limiting examples of peptidic Factor Xa inhibitors which may be used in the present invention are listed below with their CAS RN (Chemical abstract services registry number). These include Proteinase inhibitor, antistasin, CAS RN 110119-38-5; tick anticoagulant peptide, (Proteinase inhibitor, TAP) CAS RN 129737-17-3; ecotin, (Proteinase inhibitor, ecotin) CAS RN 87928-05; argasin, CAS RN 53092-89-0 ;ancylostomatin , CAS RN 11011-09-9; Ixodidae (as described in Markwardt, 1994).

[00138] Low molecular weight heparins refer to agents derived from heparins which reduces the incidence of bleeding when compared with standard heparin. Heparins are glycosaminoglycans. MW range from 2000-10000. They may be produced from porcine intestinal mucosa and except for nadroparan, are all sodium salts. A suitable heparinoid of the present invention includes but is not limited to enoxaparin, nardroparin, dalteparin, certroparin, parnaparin, reviparin, tinzaparin and combinations thereof.

[00139] Heparinoid is a modified form of heparin which reduces the incidence of bleeding when compared with standard heparin. A suitable heparinoid of the present invention includes but is not limited to Danaparoid CAS RN 308068-55-5, (e.g., Orgaran Injection Organon).

Hormone replacement agents/compositions

[00140] The compounds described herein can be used in therapeutic combination with one or more hormone replacement agents/compositions including, but not limited to androgens, estrogens, progestins, their pharmaceutically acceptable salts and derivatives thereof. Examples of androgen and estrogen combinations include but are not limited to the combination of esterified estrogens (sodium estrone sulfate and sodium equilin sulfate) and methyltestosterone (17-hydroxy-17-methyl-, (17B)-androst-4-en-3-one) available from Solvay Pharmaceuticals, Inc., Marietta, Ga., under the tradename Estratest. Examples of estrogens and estrogen combinations include but are not limited to: (a) the blend of nine (9) synthetic estrogenic substances including sodium estrone sulfate, sodium equilin sulfate, sodium 17α-dihydroequilin sulfate, sodium 17α-estradiol sulfate, sodium 17β-dihydroequilin sulfate, sodium 17 α

-dihydroequilenin sulfate, sodium 17β-dihydroequilenin sulfate, sodium equilenin sulfate and sodium 17β- estradiol sulfate; available from Duramed Pharmaceuticals, Inc., Cincinnati, Ohio, under the tradename Cenestin; (b) ethinyl estradiol (19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol; available by Schering Plough Corporation, Kenilworth, N.J., under the tradename Estinyl; (c) esterified estrogen combinations such as sodium estrone sulfate and sodium equilin sulfate; available from Solvay under the tradename Estratab and from Monarch Pharmaceuticals, Bristol, Tenn., under the tradename Menest; (d) estropipate (piperazine estra-1,3,5(10)-trien-17-one, 3-(sulfooxy)-estrone sulfate); available from Pharmacia & Upjohn, Peaack, N.J., under the tradename Ogen and from Women First Health Care, Inc., San Diego, Calif., under the tradename Ortho-Est; and (e) conjugated estrogens (17α-dihydroequilin, 17α-estradiol, and 17β.-dihydroequilin); available from Wyeth-Ayerst Pharmaceuticals, Philadelphia, Pa., under the tradename Premarin. Examples of progestin and estrogen combinations include but are not limited to: (a) the combination of estradiol (estra-1,3,5 (10)-triene-3,17β-diol hemihydrate) and norethindrone (17β- acetoxy-19-nor-17α-pregn-4-en-20-yn-3-one); which is available from Pharmacia & Upjohn, Peapack, N.J., under the tradename Activella; (b) the combination of levonorgestrel (d(-)-13β-ethyl-17α-ethinyl-17β-hydroxygon-4-en-3-one) and ethinyl estradial; available from Wyeth-Ayerst under the tradename Alesse, from Watson Laboratories, Inc., Corona, Calif., under the tradenames Levora and Trivora, Monarch Pharmaceuticals, under the tradename Nordette, and from Wyeth-Ayerst under the tradename Triphasil; (c) the combination of ethynodiol diacetate (19-nor-17α-pregn-4-en-20-yne-3β,17-diol diacetate) and ethinyl estradiol; available from G.D. Searle & Co., Chicago, Ill., under the tradename Demulen and from Watson under the tradename Zovia; (d) the combination of desogestrel (13-ethyl-11-methylene-18,19-dinor-17 α-pregn-4-en-20-yn-17-ol) and ethinyl estradiol; available from Organon under the tradenames Desogen and Mircette, and from Ortho-McNeil Pharmaceutical, Raritan, N.J., under the tradename Ortho-Cept; (e) the combination of norethindrone and ethinyl estradiol; available from Parke-Davis, Morris Plains, N.J., under the tradenames Estrostep and femhrt, from Watson under the tradenames Microgestin, Necon, and Tri-Norinyl, from Ortho-McNeil under the tradenames

Modicon and Ortho-Novum, and from Warner Chilcott Laboratories, Rockaway, N.J., under the tradename Ovcon; (f) the combination of norgestrel ((±)-13-ethyl-17-hydroxy-18,19-dinor-17α- preg-4-en-20-yn-3-one) and ethinyl estradiol; available from Wyeth-Ayerst under the tradenames Ovral and Lo/Ovral, and from Watson under the tradenames Ogestrel and Low-Ogestrel; (g) the combination of norethindrone, ethinyl estradiol, and mestranol (3-methoxy-19-nor-17α-pregna-1,3,5(110)-trien-20-yn-17-ol); available from Watson under the tradenames Brevicon and Norinyl; (h) the combination of 17β-estradiol (estra-1,3,5(10)-triene-3- ,17β-diol) and micronized norgestimate (17α-17-(Acetyloxyl)-13- ethyl-18,19-dinorpregn-4-en-20-yn-3-one3-oxime); available from Ortho-McNeil under the tradename Ortho-Prefest; (i) the combination of norgestimate (18,19-dinor-17-pregn-4-en-20-y- n-3-one, 17-(acetyloxy)-1 3-ethyl-,oxime, (17(α)-(+)-) and ethinyl estradiol; available from Ortho-McNeil under the tradenames Ortho Cyclen and Ortho Tri-Cyclen; and (j) the combination of conjugated estrogens (sodium estrone sulfate and sodium equilin sulfate) and medroxyprogesterone acetate (20-dione, 17-(acetyloxy)-6-methyl-, (6(α))-pregn-4-ene-3); available from Wyeth-Ayerst under the tradenames Premphase and Prempro. Examples of progestins include norethindrone; available from ESI Lederle, Inc., Philadelphia, Pa., under the tradename Aygestin, from Ortho-McNeil under the tradename Micronor, and from Watson under the tradename Nor-QD; norgestrel; available from Wyeth-Ayerst under the tradename Ovrette; micronized progesterone (pregn-4-ene-3, 20-dione); available from Solvay under the tradename Prometrium; and medroxyprogesterone acetate; available from Pharmacia & Upjohn under the tradename Provera. Tests showing the efficacy of the therapy and the rationale for the combination therapy with hormone replacement agents/compositions are presented in US20030119796.

Chemotherapeutic agents

[00141] The compounds described herein can be used in therapeutic combination with one or more chemotherapeutic agents including but not limited to hydrophobic, and heterocyclic cancer chemotherapeutic agents such as adriamycin (doxorubicin), phosphates, colcemid, etoposide, paclitaxel, bisantene, vincristine, and vinblastine.

Tests showing the efficacy of the therapy and the rationale for the combination therapy with chemotherapeutic agents are described, for example, in WO05/030225.

Peptide which mitigate one or more symptoms of atherosclerosis

[00142] The compounds described herein can be used in therapeutic combination with a the peptide which mitigates one or more symptoms of atherosclerosis as described, for example, in US20040266671, US6664230, US20030045460, US20030171277, US20030229015, US20040254120, US20050164950, WO/04034977, WO/02015923, and WO/05016280. This includes the peptide described as SEQ ID NO. 5 in US6664230 (CAS registry No. 631959-47-2) wherein at least one residue comprises a D-amino acid.

Anti-cancer agents

[00143] The compounds described herein can be used in therapeutic combination with an anti-cancer agent, including but not limited to: steroidal or non steroidal antiandrogens (such as finasteride (Proscar®), cyproterone acetate (CPA), flutamide (4'-nitro-3'-trifluorormethyl isobutyranilide), bicalutamide (Casodex®), and nilutamide), estrogens, diethylstilbestrol (DES), conjugated estrogens (such as Premarin®), Taxanes (such as paclitaxel (Taxol®), docetaxel (Taxotere®), 7-O-methylthio-methylpaclitaxel (disclosed in US5646176), 3'-tert-butyl-3'-N-tert-butyloxycarbonyl-4-deacetyl-3'-dephenyl-3'-N-debenzoyl-4-O-methoxycarbonyl-paclitaxel (disclosed in U.S. Ser. No. 60/179,965, and example 17 therein), C-4 methyl carbonate paclitaxel (disclosed in WO 94/14787), and formulations containing taxanes, for examples those disclosed in US6395770, US6380405, and US6239167), epothilones (such as epothilone A, epothilone B, epothilone C, epothilone D, desoxyepothilone A, desoxyepothilone B, [1S-[1R*,3R*(E),7R*,10S*, 11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2- -methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]hepta-decane-5,9-dione (disclosed in WO 99/02514), [1S-[1R*,3R*(E),7R*,10S*,11R*12R *,16S *]]-3-[2-[2-(aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8- ,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]-heptadecane-5,9-dione (disclosed in U.S. Ser.

No. 09/506,481 filed on Feb. 17, 2000, and examples 7 and 8 therein), and derivatives thereof), microtuble-disruptor agents, alkylating agents, anti-metabolites, epidophyllotoxin, an antineoplastic enzyme, a topoisomerase inhibitor, procarbazine, mitoxantrone, platinum coordination complexes, biological response modifiers, growth inhibitors, hormonal/antihormonal therapeutic agents, haematopoietic growth factors, the anthracycline family of drugs, vinca drugs, mitomycins, bleomycins, cytotoxic nucleosides, discodermolide, the pteridine family of drugs, diynenes, aromatase inhibitors, podophyllotoxins, doxorubicin, carminomycin, daunorubicin, idarubicin, dactinomycin, plicamycin, vinorelbine, aminopterin, methotrexate, methopterin, dichloro-methotrexate, thioguanine, hydroxyrurea, campathecins, nitrosureas, mitomycin C, porfiromycin, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, podophyllotoxin or podophyllotoxin derivatives such as etoposide, etoposide phosphate or teniposide, melphalan, vinblastine, vincristine, leurosidine, vindesine, leurosine, estramustine, cisplatin, carboplatin, cyclophosphamide, bleomycin, tamoxifen, ifosfamide, melphalan, hexamethyl melamine, thiotepa, cytarabin, idatrexate, trimetrexate, dacarbazine, L-asparaginase, camptothecin, CPT-11, topotecan, ara-C, bicalutamide, flutamide, leuprolide, pyridobenzoindole derivatives, interferons, interleukins, LHRH analogs (such as goserelin acetate (Zoladex®) and leuprolide acetate (Lupron®)), and selective estrogen receptor modulator (SERM) compounds. The term selective estrogen receptor modulator includes both estrogen agonist and estrogen antagonists and refers to compounds that bind with the estrogen receptor, inhibit bone turnover and prevent bone loss. In particular, estrogen agonists are compounds capable of binding to the estrogen receptor sites in mammalian tissue, and mimicking the actions of estrogen in one or more tissue. Estrogen antagonists are compounds capable of binding to the estrogen receptor sites in mammalian tissue, and blocking the actions of estrogen in one or more tissues.

[00144] SERMs include but are not limited to tamoxifen (and associated compounds disclosed in US4536516); 4-hydroxytamoxifen (and associated compounds disclosed in US4623660); raloxifene (and associated compounds disclosed in US4418068, US5393763, US5457117, US5478847, and US5641790);

droloxifene; idoxifene (and associated compounds disclosed in US4839155); lasofoxifene; TSE-424 (and other compounds disclosed in US5998402, US5985910, US5780497, US5880137, EP0802183A1); LY353381; LY117081; toremifene (and other compounds disclosed in US4696949 and US4996225); centchroman (and other compounds disclosed in US3822287); fulvestrant; 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate; 4,4'-dihydroxybenzophenone-2,4-dinitrophenylhydrazone; SH646; 6-(4-hydroxy-phenyl)-5-[4-(2-piperidin-1-yl-etho- xy)-benzyl]-naphthalen-2-ol (and other compounds as disclosed in US5484795); {4-[2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-phenyl}-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl]-methanone; GW 5638; GW 7604; EM-652 and EM-800 (synthesis and activity described in Gauthier et al., (1997) J. Med. Chem. 40:2117-2122); those compounds disclosed in US552412 (including cis-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,- 7,8-tetrahydro-naphthalene-2-ol; (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-te- trahydro-naphthalene-2-ol; cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; cis-1-[6'-pyrrolidinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene; 1-(4'-pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,- 4-tetrahydroisoquinoline; cis-6-(4-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,- 7,8-tetrahydro-naphthalene-2-ol; 1-(4'-pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline and the tartrate salt thereof (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl-]-5,6,7,8-tetrahydro-naphthalene-2-ol), US20040259886, US20040162304, and WO95/10513; and pharmaceutically acceptable salts and esters thereof. Tests showing the efficacy of the therapy and the rationaled for the combination therapy with an anticancer agent are presented in US20040116358 and WO04/010948.

Agents used to treat bone loss and associated disorders

[00145] The compounds described herein can be used in therapeutic combination with an agent used to treat bone loss and associated disorders including but not limited to: (1) SERMs (including those described above); (2) bisphosphonates including but

not limited to alendronic acid and alendronate/MK-217/(Fosamax®)/alendronate sodium/alendronate monosodium trihydrate including sodium, potassium, calcium, magnesium or ammonium salts thereof (alendronic acid and alendronate are disclosed in US4922007, US5019651, US5510517, and US564849)1; also); Yamanouchi compound YM 175/incadronate/cimadronate (cycloheptylaminomethylene-1,1-bisphosphonic acid, US4970335); 1,1-dichloromethylene-1,1-diphosphonic acid (clodronic acid), and the disodium salt (clodronate, Procter and Gamble), as described in Belgium Patent 672,205 (1966) and J. Org. Chem 32, 4111 (1967)); EB-1053(1-hydroxy-3-(1-pyrrolidinyl)-propylidene-1,1-bisphosphonic acid); etidronic acid (1-hydroxyethane-1,1-diphosphonic acid (etidronic acid); Boehringer-Mannheim compound ibandronate/BM-210955 (1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid; disclosed in US4927814); minodronate (1-hydroxy-2-imidazo-(1,2-a)pyridin-3-yethylidene); neridronate (6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid); olpadronate (3-(dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid); pamidronate (3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid); piridronate (2-(2-pyridinyl)ethylidene]-1,1-bisphosphonic acid; described in US4761406); risedronate (1-hydroxy-2-(3-pyridinyl)-ethylidene-1,1-bisphosphonic acid); tiludronate (4-chlorophenyl)thiomethane-1,1-disphosphonic acid; described in US4876248); zoledronate (1-hydroxy-2-(1H-imidazol-1-yl)ethylidene-1,1-bisphosphonic acid); etidronate; and pharmaceutically acceptable salts and esters thereof; and also including mixtures thereof; (3) estrogens and estrogen combinations (including those described above); (4) cathepsin K inhibitors (e.g., compounds which interfere with the activity of the cysteine protease cathepsin K) including those disclosed in WO00/55126 and WO01/49288; (5) androgen receptor modulators including but not limited to finasteride and other 5α-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate; (6) inhibitors of osteoclast proton ATPase including those described in Farina et al. (1999) DDT, 4:163-172; *(7)* HMG-CoA reductase inhibitors (including those described above); (8) integrin receptor antagonists (including those described in US20040162304); (9) osteoblast anabolic agents (e.g., agents that build bone such as parathyroid horomone (PTH) or its amino

terminal fragments (PTHrP-(1-36); Syed et al. (2001) JCEM 86:1525-1531) and analogues); (10) calcitonin; (11) vitamin D which includes, but is not limited to, vitamin D_3 (cholecalciferol), vitamin D_2 (ergocalciferol);1α-hydroxy vitamin D;25-hydroxy vitamin D;1α,25-dihydroxy vitamin D; and dihydroxy vitamin D; (12) synthetic vitamin D analogues (non-naturally occurring compounds that act like vitamin D); (13) compounds disclosed in US5280040; and (14) serotonin reuptake inhibitors (including those described above).

[00146] The compounds described herein can be used in therapeutic combination with other agents including but not limited to: a thromboxane A2 (TxA2) antagonist; a CRTH2 receptor modulator (such as Ramatroban/Baynas/BAY u3405 which exhibits both TxA2 and CRTH2 antagonistic activity); ranitine; bosentan; a tyrosine kinase inhibitor such as disclosed in WO00/053605; a selective androgen receptor modulator (SARM) inlcuding LGD-2226 (Ligand) or those compounds disclosed in WO03/011824; coenzyme Q10 such as disclosed in US5316765, US4933165, and US4929437; an agent that upregulates type III endothelial cell nitric acid syntase such as disclosed in WO00/003746; a chondroprotective compound such as a polysulfated glycosaminoglycan (PSGAG), glucosamine, chondroitin sulfate (CS), hyaluronic acid (HA), pentosan polysulfate (PPS), doxycycline or minocycline, such as disclosed in EP970694; monocyte and macrophage inhibitors such as polyunsaturated fatty acids (PUFA); thyroid hormones including throxine analogues (such as CGS-26214 (a thyroxine compound with a fluorinated ring),dextrothyroxine, eitroxate, and thyropropic acid;. a 5-HT reuptake inhibitor such as disclosed in WO99/44609; and anti-infective agents such as quinolones, for example, ciprofloxacin, ofloxacin, and Tequin™ (Bristol-Myers Squibb), macrolides such as erythromycin and clarithromycin (Biaxin™ (Abbott)), and azithromycin (Zithromax (Pfizer)). The compounds described herein can be used in therapeutic combination with interleukin-6 modulators including those described in US20060078533 such as interleukin-6 inhibitors/antibodies, interleukin-6 receptor inhibitors/antibodies, interleukin-6 antisense oligonucleotide (ASON), gp130 protein inhibitors/antibodies, tyrosine kinases inhibitors/antibodies, serine/threonine kinases inhibitors/antibodies, mitogen-activated protein (MAP) kinase inhibitors/antibodies, phosphatidylinositol 3-kinase

(PI3K) inhibitors/antibodies, Nuclear factor κB (NF-κB) inhibitors/antibodies, IκB kinase (IKK) inhibitors/antibodies, activator protein-1 (AP-1) inhibitors/antibodies, STAT transcription factors inhibitors/antibodies, altered IL-6, partial peptides of IL-6 or IL-6 receptor, and SOCS (suppressors of cytokine signaling) protein. The compounds described herein can be used in therapeutic combination with at least one ubiquinone (e.g. Coenzyme Q, Coenzyme Q_{10}). In certain embodiments, a compound described herein is coadministered with a statin (e.g. atorvastatin, atorvastatin calcium, rosuvastatin, rosuvastatin calcium) and a ubiquinone (e.g. e.g. Coenzyme Q, Coenzyme Q_{10}). The compounds described herein can be used in therapeutic combination with a PGD2 receptor 1 (DP1, also called DP-1, DP) antagonist such as MK-0524 (Merck) and those described in patent publications, WO06026273. In certain embodiments, a compound described herein is coadministered with nicotinic acid or niacin (including derivatives and extended release formulations (e.g., Niaspan®) thereof) and a DP1 antagonist (e.g. MK-0524).

[00147] It can be useful to administer a compound described herein together with 1, 2, 3, or more of an HMG-CoA reductase inhibitor (e.g., a statin such as atorvastatin, atorvastatin calcium, rosuvastatin, rosuvastatin calcium, simvastatin), a fibrate (e.g., fenofibrate(Tricor®)), niacin (including derivatives and extended release formulations (e.g., Niaspan®) thereof), a glitazone (e.g., rosiglitazone maleate (Avandia®), piogilitazone hydrochloride(Actos®)), a calcium channel blocker (e.g., amlodipine besylate (Norvasc®)), an angiotensin II receptor antagonist (e.g., valsartan (Diovan®, Diovan HCT® (valsartan and hydrochlorothiazide))), a biguanide (e.g., metformin (Glucophage®)), a sulfonylurea (e.g., glipizide (Glucotrol®, Glucotrol XL®), glyburide (Micronase®, Glynase Prestab®, Diabeta®), and Glucovance® (glyburide and metformin). It can be particularly useful to combine a compound described herein together with one or more of an HMG-CoA reductase inhibitor (e.g., a statin), a fibrate, a glitazone, niacin or a derivative thereof, a calcium channel blocker, an angiotensin II receptor antagonist, a biguanide, a sulfonylurea in a single pharmaceutical composition. The precise amount of each of the two or more active ingredients in a dosage unit will depend on the desired dosage of each component. Thus, it can be useful to create a dosage unit that will, when administered according to

a particular dosage schedule (e.g., a dosage schedule specifying a certain number of units and a particular timing for administration), deliver the same dosage of each component as would be administered if the patient was being treated with only a single component. In other circumstances, it might be desirable to create a dosage unit that will deliver a dosage of one or more components that is less than that which would be administered if the patient was being treated only with a single component. Finally, it might be desirable to create a dosage unit that will deliver a dosage of one or more components that is greater than that which would be administered if the patient was being treated only with a single component. The pharmaceutical composition can include additional ingredients including but not limited to the excipients described herein. In certain embodiments, one or more therapeutic agents of the dosage unit may exist in an extended or control release formulation and additional therapeutic agents may not exist in extended release formulation. For example, a compound described herein may exist in the same dosage unit with fenofibrate (an extended release fibrate agent). For example, a compound described herein may exist in the same dosage unit with one or more additional agents including a controlled release formulation of torcetrapib.

[00148] A pharmaceutical composition can include 1% to 20% by weight of a compound described herein; from 1% to 80% by weight of an HMG-CoA reductase inhibitor such as atorvastatin, atorvastatin calcium, dihydrocompactin, bervastatin, carvastatin, cerivastatin, crilvastatin, dalvastatin, fluvastatin, glenvastatin, fluindostatin, velostatin, lovastatin, mevastatin, compactin, pitavastatin, pravastatin, rivastatin, rosuvastatin, rosuvastatin calcium, simvastatin, sirrivastatin, and CI-981; and from 0.01% to 2% by weight of a stabilizing agent such as butylated hydroxyanisole (BHA). It further can include from 1% to 80% by weight of microcrystalline cellulose; from 0.5% to 10% by weight of hydroxypropyl methylcellulose; from 0.1% to 4% by weight of magnesium stearate; and from 25% to 70% by weight of lactose. The composition may optionally include one or more of croscarmellose sodium, citric acid, ascorbic acid and propyl gallate. The composition can include or exclude one or more of citric acid, ascorbic acid and pre-gelatinized

starch. As a practical matter, a single dosage unit such as a tablet or capsule should weigh from 50 mg to 1000 mg (for example, including from 100 mg to 800 mg).

[00149] A dosage unit (e.g., an oral dosage unit) can include from, for example, 1 to 500 mg, 2 mg to 500 mg, 1 to 300 mg, 1 to 100 mg, 5 mg to 100 mg, 1 to 30 mg, 1 to 40 mg, 5 mg to 20 mg, 1 mg, 2 mg, 3 mg, 4mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, and 100 mg of a compound described herein; from 5 mg to 80 mg (e.g., 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 60 mg, 70 mg and 80 mg) of a statin (e.g., atorvastatin, atorvastatin calcium, rosuvastatin, rosuvastatin calcium, simvastatin, etc.); and from 0.002 mg to 0.004 mg of BHA per mg of statin. In certain embodiments, the dosage unit comprises 5 mg of a compound described herein and 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80 mg of a statin. In certain embodiments, the dosage unit comprises 10 mg of a compound described herein and 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80 mg of a statin. In certain embodiments, the dosage unit comprises 15 mg of a compound described herein and 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80 mg of a statin. In certain embodiments, the dosage unit comprises 20 mg of a compound described herein and 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80 mg of a statin. In certain embodiments, the dosage unit comprises 25 mg of a compound described herein and 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80 mg of a statin. In certain embodiments, the dosage unit comprises 30 mg of a compound described herein and 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80 mg of a statin. In certain embodiments, the dosage unit comprises 35 mg of a compound described herein and 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80 mg of a statin. In certain embodiments, the dosage unit comprises 40 mg of a compound described herein and 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80 mg of a statin. In certain embodiments, the dosage unit comprises 45 mg of a compound described herein and 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80 mg of a statin. In certain embodiments, the dosage unit comprises 50 mg of a compound described herein and 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80 mg

of a statin. In certain embodiments, the dosage unit comprises 55 mg of a compound described herein and 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80 mg of a statin. In certain embodiments, the dosage unit comprises 60 mg of a compound described herein and 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80 mg of a statin. In certain embodiments, the dosage unit comprises 65 mg of a compound described herein and 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80 mg of a statin. In certain embodiments, the dosage unit comprises 70 mg of a compound described herein and 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80 mg of a statin. In certain embodiments, the dosage unit comprises 75 mg of a compound described herein and 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80 mg of a statin. In certain embodiments, the dosage unit comprises 80 mg of a compound described herein and 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80 mg of a statin. In certain embodiments, the dosage unit comprises 85 mg of a compound described herein and 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80 mg of a statin. In certain embodiments, the dosage unit comprises 90 mg of a compound described herein and 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80 mg of a statin. In certain embodiments, the dosage unit comprises 95 mg of a compound described herein and 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80 mg of a statin. In certain embodiments, the dosage unit comprises 100 mg of a compound described herein and 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80 mg of a statin. A daily dose can include 5-100 mg (e.g., 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg) of a compound described herein and 5, 10, 20, 30, 40, 50, 60, 70 or 80 mg of a statin. In certain embodiments the statin is selected from the group consisting of atorvastatin, atorvastatin calcium, rosuvastatin, rosuvastatin calcium and simvastatin. In certain embodiments the statin is atorvastatin. In certain embodiments thereof the daily dosage unit can include 5-100 mg (e.g., 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg) of a compound described herein and 10 mg, 20 mg, 40 mg, or 80 mg of atorvastatin. In certain embodiments the statin is rosuvastatin (e.g. rosuvastatin calcium). In certain embodiments thereof the daily dosage unit can include 5-100 mg (e.g., 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg) of a compound described herein and 5 mg, 10 mg, 20 mg, or 40 mg of

rosuvastatin (e.g. rosuvasatin calcium). In certain embodiments the dosage unit and daily dose are equivalent. In various embodiments, the dosage unit is administered with food at anytime of the day, without food at anytime of the day, with food after an overnight fast (e.g., with breakfast), at bedtime after a low fat snack. In various embodiments, the dosage unit is administered once a day, twice a day, three times a day, four times a day. The dosage unit can include from 0.0005 mg to 0.001 mg of propyl gallate per mg of statin. For example, the dosage unit can include from 0.01 mg to 16 mg, and particularly from 0.02 mg to 0.16 mg of BHA, and additionally may be include from 0.001 mg to 0.05 mg, and particularly from 0.005 mg to 0.04 mg of propyl gallate. The dosage unit can additionally include from 1 mg to 640 mg, and particularly from 15 mg to 120 mg of microcrystalline cellulose; from 0.5 mg to 80 mg, and particularly from 2 mg to 16 mg of HPMC; from 0.1 mg to 32 mg, and particularly from 1.5 to 12 mg of magnesium stearate; and lactose. Croscarmellose sodium may optionally be included as a component in the composition. For example, an oral dosage unit may contain from 0 mg to 80 mg of croscarmellose sodium, and particularly from 3 mg to 24 mg of croscarmellose sodium. Citric acid may optionally be included as a component in the composition. For example, an oral dosage unit may contain from 0 mg to 80 mg, and particularly from 0.25 mg to 2 mg of citric acid. In addition, one or more of lactic acid, malic acid, succinic acid, tartaric acid and EDTA may optionally be included in the dosage unit. An inert component such as lactose can be added to bring the unit dosage form to a desired total weight. The dosage unit can optionally comprise other agents such as 1, 2, 3, or more of a fibrate, niacin (including derivatives thereof), a glitazone, a calcium channel blocker, an angiotensin II receptor antagonist, a biguanide, a CETP inhibitor, a probucol derivative, and a sulfonylurea.

[00150] A dosage unit (e.g., an oral dosage unit) can include, for example, from 1 to 500 mg, 2 mg to 500 mg, 1 to 300 mg, 1 to 100 mg, 5 mg to 100 mg, 1 to 30 mg, 1 to 40 mg, 5 mg to 20 mg, 1 mg, 2 mg, 3 mg, 4mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, and 100 mg of a compound described herein and from 10 mg to 150 mg (e.g., 10 mg, 20 mg, 30 mg, 40 mg, 48 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90

mg, 100 mg, 120 mg, 130 mg, 140 mg, 145 mg, 150 mg) of a fibrate (e.g., fenofibrate (Tricor®). In certain embodiments, the dosage unit comprises 5 mg of a compound described herein and 10, 20, 30, 40, 48, 50, 60, 70, 80, 90, 100, 120, 130, 140, 145, or 150 mg of a fibrate. In certain embodiments, the dosage unit comprises 10 mg of a compound described herein and 10, 20, 30, 40, 48, 50, 60, 70, 80, 90, 100, 120, 130, 140, 145, or 150 mg of a fibrate. In certain embodiments, the dosage unit comprises 15 mg of a compound described herein and 10, 20, 30, 40, 48, 50, 60, 70, 80, 90, 100, 120, 130, 140, 145, or 150 mg of a fibrate. In certain embodiments, the dosage unit comprises 20 mg of a compound described herein and 10, 20, 30, 40, 48, 50, 60, 70, 80, 90, 100, 120, 130, 140, 145, or 150 mg of a fibrate. In certain embodiments, the dosage unit comprises 25 mg of a compound described herein and 10, 20, 30, 40, 48, 50, 60, 70, 80, 90, 100, 120, 130, 140, 145, or 150 mg of a fibrate. In certain embodiments, the dosage unit comprises 30 mg of a compound described herein and 10, 20, 30, 40, 48, 50, 60, 70, 80, 90, 100, 120, 130, 140, 145, or 150 mg of a fibrate. In certain embodiments, the dosage unit comprises 35 mg of a compound described herein and 10, 20, 30, 40, 48, 50, 60, 70, 80, 90, 100, 120, 130, 140, 145, or 150 mg of a fibrate. In certain embodiments, the dosage unit comprises 40 mg of a compound described herein and 10, 20, 30, 40, 48, 50, 60, 70, 80, 90, 100, 120, 130, 140, 145, or 150 mg of a fibrate. In certain embodiments, the dosage unit comprises 45 mg of a compound described herein and 10, 20, 30, 40, 48, 50, 60, 70, 80, 90, 100, 120, 130, 140, 145, or 150 mg of a fibrate. In certain embodiments, the dosage unit comprises 50 mg of a compound described herein and 10, 20, 30, 40, 48, 50, 60, 70, 80, 90, 100, 120, 130, 140, 145, or 150 mg of a fibrate. In certain embodiments, the dosage unit comprises 55 mg of a compound described herein and 10, 20, 30, 40, 48, 50, 60, 70, 80, 90, 100, 120, 130, 140, 145, or 150 mg of a fibrate. In certain embodiments, the dosage unit comprises 60 mg of a compound described herein and 10, 20, 30, 40, 48, 50, 60, 70, 80, 90, 100, 120, 130, 140, 145, or 150 mg of a fibrate. In certain embodiments, the dosage unit comprises 65 mg of a compound described herein and 10, 20, 30, 40, 48, 50, 60, 70, 80, 90, 100, 120, 130, 140, 145, or 150 mg of a fibrate. In certain embodiments, the dosage unit comprises 70 mg of a compound described herein and 10, 20, 30, 40, 48, 50, 60, 70, 80, 90, 100, 120, 130, 140, 145, or 150 mg of

a fibrate. In certain embodiments, the dosage unit comprises 75 mg of a compound described herein and 10, 20, 30, 40, 48, 50, 60, 70, 80, 90, 100, 120, 130, 140, 145, or 150 mg of a fibrate. In certain embodiments, the dosage unit comprises 80 mg of a compound described herein and 10, 20, 30, 40, 48, 50, 60, 70, 80, 90, 100, 120, 130, 140, 145, or 150 mg of a fibrate. In certain embodiments, the dosage unit comprises 85 mg of a compound described herein and 10, 20, 30, 40, 48, 50, 60, 70, 80, 90, 100, 120, 130, 140, 145, or 150 mg of a fibrate. In certain embodiments, the dosage unit comprises 90 mg of a compound described herein and 10, 20, 30, 40, 48, 50, 60, 70, 80, 90, 100, 120, 130, 140, 145, or 150 mg of a fibrate. In certain embodiments, the dosage unit comprises 95 mg of a compound described herein and 10, 20, 30, 40, 48, 50, 60, 70, 80, 90, 100, 120, 130, 140, 145, or 150 mg of a fibrate. In certain embodiments, the dosage unit comprises 100 mg of a compound described herein and 10, 20, 30, 40, 48, 50, 60, 70, 80, 90, 100, 120, 130, 140, 145, or 150 mg of a fibrate. A daily dose can include 5-100 mg (e.g., 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg) of a compound described herein and 10, 20, 30, 40, 48, 50, 60, 70, 80, 90, 100, 120, 130, 140, 145, or 150 mg of a fibrate. In certain embodiments, the fibrate is fenofibrate (Tricor®). In certain embodiments the dosage unit includes 5-100 mg (e.g., 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg) of a compound described herein and 48 mg, 96 mg or 145 mg of fenofibrate (e.g. Tricor®). In certain embodiments the dosage unit and daily dose are equivalent. In various embodiments, the dosage unit is administered with food at anytime of the day, without food at anytime of the day, with food after an overnight fast (e.g., with breakfast), at bedtime after a low fat snack. In various embodiments, the dosage unit is administered once a day, twice a day, three times a day, four times a day. The dosage unit can optionally comprise other agents such as 1, 2, 3, or more of an HMG CoA reductase inhibitor (e.g.a statin), niacin (including derivatives thereof), a glitazone, a calcium channel blocker, an angiotensin II receptor antagonist, a biguanide, a CETP inhibitor, a probucol derivative and a sulfonylurea.

[00151] A dosage unit (e.g., an oral dosage unit) can include, for example, from 1 to 500 mg, 2 mg to 500 mg, 1 to 300 mg, 1 to 100 mg, 5 mg to 100 mg, 1 to 30 mg, 1 to 40 mg, 5 mg to 20 mg, 1 mg, 2 mg, 3 mg, 4mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg,

11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, and 100 mg of a compound described herein and from 1 mg to 60 mg (e.g., 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 60 mg) of a glitazone (e.g., rosiglitazone, pioglitazone). In certain embodiments, the dosage unit comprises 5 mg of a compound described herein and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, or 60 mg of a glitazone. In certain embodiments, the dosage unit comprises 10 mg of a compound described herein and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, or 60 mg of a glitazone. In certain embodiments, the dosage unit comprises 15 mg of a compound described herein and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, or 60 mg of a glitazone. In certain embodiments, the dosage unit comprises 20 mg of a compound described herein and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, or 60 mg of a glitazone. In certain embodiments, the dosage unit comprises 25 mg of a compound described herein and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, or 60 mg of a glitazone. In certain embodiments, the dosage unit comprises 30 mg of a compound described herein and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, or 60 mg of a glitazone. In certain embodiments, the dosage unit comprises 35 mg of a compound described herein and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, or 60 mg of a glitazone. In certain embodiments, the dosage unit comprises 40 mg of a compound described herein and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, or 60 mg of a glitazone. In certain embodiments, the dosage unit comprises 45 mg of a compound described herein and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, or 60 mg of a glitazone. In certain embodiments, the dosage unit comprises 50 mg of a compound described herein and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, or 60 mg of a glitazone. In certain embodiments, the dosage unit comprises 55 mg of a compound described herein and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, or 60 mg of a glitazone. In certain embodiments, the dosage unit comprises 60

mg of a compound described herein and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, or 60 mg of a glitazone. In certain embodiments, the dosage unit comprises 65 mg of a compound described herein and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, or 60 mg of a glitazone. In certain embodiments, the dosage unit comprises 70 mg of a compound described herein and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, or 60 mg of a glitazone. In certain embodiments, the dosage unit comprises 75 mg of a compound described herein and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, or 60 mg of a glitazone. In certain embodiments, the dosage unit comprises 80 mg of a compound described herein and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, or 60 mg of a glitazone. In certain embodiments, the dosage unit comprises 85 mg of a compound described herein and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, or 60 mg of a glitazone. In certain embodiments, the dosage unit comprises 90 mg of a compound described herein and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, or 60 mg of a glitazone. In certain embodiments, the dosage unit comprises 95 mg of a compound described herein and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, or 60 mg of a glitazone. In certain embodiments, the dosage unit comprises 100 mg of a compound described herein and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, or 60 mg of a glitazone. A daily dose can include 5-100 mg (e.g., 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg) of a compound described herein and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, or 60 mg of a glitazone. In certain embodiments the glitazone is rosiglitazone maleate (Avandia®). In certain embodiments the glitazone is pioglitazone (Actos®). In certain embodiments the dosage unit and daily dose are equivalent. In various embodiments, the dosage unit is administered with food at anytime of the day, without food at anytime of the day, with food after an overnight fast (e.g., with breakfast), at bedtime after a low fat snack. In various embodiments, the dosage unit is administered once a day, twice a day, three times a day, four times a day. The dosage unit can optionally comprise other agents such as 1, 2, 3, or more of an HMG CoA reductase inhibitor (e.g.a statin), a fibrate, niacin (including derivatives thereof), a

calcium channel blocker, an angiotensin II receptor antagonist, a biguanide, a CETP inhibitor, a probucol derivative and a sulfonylurea.

[00152] A dosage unit (e.g., an oral dosage unit) can include, for example, from 1 to 500 mg, 2 mg to 500 mg, 1 to 300 mg, 1 to 100 mg, 5 mg to 100 mg, 1 to 30 mg, 1 to 40 mg, 5 mg to 20 mg, 1 mg, 2 mg, 3 mg, 4mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, and 100 mg of a compound described herein and from 100 mg to 2000 mg (e.g., 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, 2000 mg) of niacin or a derivative thereof. In certain embodiments, the dosage unit comprises 5 mg of a compound described herein and 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg of niacin or a derivative thereof. In certain embodiments, the dosage unit comprises 10 mg of a compound described herein and 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg of niacin or a derivative thereof. In certain embodiments, the dosage unit comprises 15 mg of a compound described herein and 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg of niacin or a derivative thereof. In certain embodiments, the dosage unit comprises 20 mg of a compound described herein and 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg of niacin or a derivative thereof. In certain embodiments, the dosage unit comprises 25 mg of a compound described herein and 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg of niacin or a derivative thereof. In certain embodiments, the dosage unit comprises 30 mg of a compound described herein and 100, 150, 200, 250, 300, 350, 400, 450, 500,

550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg of niacin or a derivative thereof. In certain embodiments, the dosage unit comprises 35 mg of a compound described herein and 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg of niacin or a derivative thereof. In certain embodiments, the dosage unit comprises 40 mg of a compound described herein and 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg of niacin or a derivative thereof. In certain embodiments, the dosage unit comprises 45 mg of a compound described herein and 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg of niacin or a derivative thereof. In certain embodiments, the dosage unit comprises 50 mg of a compound described herein and 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg of niacin or a derivative thereof. In certain embodiments, the dosage unit comprises 55 mg of a compound described herein and 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg of niacin or a derivative thereof. In certain embodiments, the dosage unit comprises 60 mg of a compound described herein and 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg of niacin or a derivative thereof. In certain embodiments, the dosage unit comprises 65 mg of a compound described herein and 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg of niacin or a derivative thereof. In certain embodiments, the dosage unit comprises 70 mg of a compound described herein and 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg of niacin or a derivative thereof. In certain embodiments, the dosage unit comprises 75 mg of a compound described herein and

100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg of niacin or a derivative thereof. In certain embodiments, the dosage unit comprises 80 mg of a compound described herein and 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg of niacin or a derivative thereof. In certain embodiments, the dosage unit comprises 85 mg of a compound described herein and 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg of niacin or a derivative thereof. In certain embodiments, the dosage unit comprises 90 mg of a compound described herein and 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg of niacin or a derivative thereof. In certain embodiments, the dosage unit comprises 95 mg of a compound described herein and 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg of niacin or a derivative thereof. In certain embodiments, the dosage unit comprises 100 mg of a compound described herein and 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg of niacin or a derivative thereof. A daily dose can include 5-100 mg (e.g., 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg) of a compound described herein and 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg of niacin or a derivative thereof. In certain embodiments the niacin derivative is Niaspan® (niacin extended release tablets). In certain embodiments the dosage unit and daily dose are equivalent. In various embodiments, the dosage unit is administered with food at anytime of the day, without food at anytime of the day, with food after an overnight fast (e.g., with breakfast), at bedtime after a low fat snack. In various embodiments, the dosage unit is administered once a day, twice a day, three times a day, four times a day. The dosage unit can optionally comprise other agents such as 1, 2, 3, or more of an HMG CoA

reductase inhibitor (e.g.a statin), a fibrate, a glitazone, a calcium channel blocker, an angiotensin II receptor antagonist, a biguanide, a CETP inhibitor, a probucol derivative and a sulfonylurea.

[00153] A dosage unit (e.g., an oral dosage unit) can include, for example, from 1 to 500 mg, 2 mg to 500 mg, 1 to 300 mg, 1 to 100 mg, 5 mg to 100 mg, 1 to 30 mg, 1 to 40 mg, 5 mg to 20 mg, 1 mg, 2 mg, 3 mg, 4mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, and 100 mg of a compound described herein and from 1 mg to 15 mg (e.g., 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 7.5 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 12.5 mg, 13 mg, 14 mg, 15 mg) of a calcium channel blocker (e.g., amlodipine). In certain embodiments, the dosage unit comprises 5 mg of a compound described herein and 1, 2, 2.5, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 11, 12, 12.5, 13, 14, or 15 mg of a calcium channel blocker. In certain embodiments, the dosage unit comprises 10 mg of a compound described herein and 1, 2, 2.5, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 11, 12, 12.5, 13, 14, or 15 mg of a calcium channel blocker. In certain embodiments, the dosage unit comprises 15 mg of a compound described herein and 1, 2, 2.5, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 11, 12, 12.5, 13, 14, or 15 mg of a calcium channel blocker. In certain embodiments, the dosage unit comprises 20 mg of a compound described herein and 1, 2, 2.5, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 11, 12, 12.5, 13, 14, or 15 mg of a calcium channel blocker. In certain embodiments, the dosage unit comprises 25 mg of a compound described herein and 1, 2, 2.5, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 11, 12, 12.5, 13, 14, or 15 mg of a calcium channel blocker. In certain embodiments, the dosage unit comprises 30 mg of a compound described herein and 1, 2, 2.5, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 11, 12, 12.5, 13, 14, or 15 mg of a calcium channel blocker. In certain embodiments, the dosage unit comprises 35 mg of a compound described herein and 1, 2, 2.5, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 11, 12, 12.5, 13, 14, or 15 mg of a calcium channel blocker. In certain embodiments, the dosage unit comprises 40 mg of a compound described herein and 1, 2, 2.5, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 11, 12, 12.5, 13, 14, or 15 mg of a calcium channel blocker. In certain embodiments, the dosage unit comprises 45 mg of a compound described herein and 1, 2, 2.5, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 11, 12, 12.5, 13, 14, or 15 mg

of a calcium channel blocker. In certain embodiments, the dosage unit comprises 50 mg of a compound described herein and 1, 2, 2.5, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 11, 12, 12.5, 13, 14, or 15 mg of a calcium channel blocker. In certain embodiments, the dosage unit comprises 55 mg of a compound described herein and 1, 2, 2.5, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 11, 12, 12.5, 13, 14, or 15 mg of a calcium channel blocker. In certain embodiments, the dosage unit comprises 60 mg of a compound described herein and 1, 2, 2.5, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 11, 12, 12.5, 13, 14, or 15 mg of a calcium channel blocker. In certain embodiments, the dosage unit comprises 65 mg of a compound described herein and 1, 2, 2.5, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 11, 12, 12.5, 13, 14, or 15 mg of a calcium channel blocker. In certain embodiments, the dosage unit comprises 70 mg of a compound described herein and 1, 2, 2.5, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 11, 12, 12.5, 13, 14, or 15 mg of a calcium channel blocker. In certain embodiments, the dosage unit comprises 75 mg of a compound described herein and 1, 2, 2.5, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 11, 12, 12.5, 13, 14, or 15 mg of a calcium channel blocker. In certain embodiments, the dosage unit comprises 80 mg of a compound described herein and 1, 2, 2.5, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 11, 12, 12.5, 13, 14, or 15 mg of a calcium channel blocker. In certain embodiments, the dosage unit comprises 85 mg of a compound described herein and 1, 2, 2.5, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 11, 12, 12.5, 13, 14, or 15 mg of a calcium channel blocker. In certain embodiments, the dosage unit comprises 90 mg of a compound described herein and 1, 2, 2.5, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 11, 12, 12.5, 13, 14, or 15 mg of a calcium channel blocker. In certain embodiments, the dosage unit comprises 95 mg of a compound described herein and 1, 2, 2.5, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 11, 12, 12.5, 13, 14, or 15 mg of a calcium channel blocker. In certain embodiments, the dosage unit comprises 100 mg of a compound described herein and 1, 2, 2.5, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 11, 12, 12.5, 13, 14, or 15 mg of a calcium channel blocker. A daily dose can include 5-100 mg (e.g., 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg) of a compound described herein and 1, 2, 2.5, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 11, 12, 12.5, 13, 14, or 15 mg of a calcium channel blocker. In certain embodiments the calcium channel blocker is amlodipine (Norvasc®; amlodipine beslylate). In certain embodiments the dosage unit and daily dose are equivalent. In various embodiments, the dosage unit is administered with food at anytime of the day,

without food at anytime of the day, with food after an overnight fast (e.g., with breakfast), at bedtime after a low fat snack. In various embodiments, the dosage unit is administered once a day, twice a day, three times a day, four times a day. The dosage unit can optionally comprise other agents such as 1, 2, 3, or more of an HMG CoA reductase inhibitor (e.g.a statin), a fibrate, niacin (including derivatives thereof), a glitazone, an angiotensin II receptor antagonist, a biguanide, a CETP inhibitor, a probucol derivative and a sulfonylurea.

[00154] A dosage unit (e.g., an oral dosage unit) can include, for example, from 1 to 500 mg, 2 mg to 500 mg, 1 to 300 mg, 1 to 100 mg, 5 mg to 100 mg, 1 to 30 mg, 1 to 40 mg, 5 mg to 20 mg, 1 mg, 2 mg, 3 mg, 4mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, and 100 mg of a compound described herein and from 20 mg to 400 mg (e.g., 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 220 mg, 240 mg, 260 mg, 280 mg, 320 mg, 340 mg, 360 mg, 380 mg, 400 mg) of an angiotensin II receptor antagonist (e.g., valsartan). In certain embodiments, the dosage unit comprises 5 mg of a compound described herein and 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 280, 320, 340, 360, 380, or 400 mg of an angiotensin II receptor antagonist. In certain embodiments, the dosage unit comprises 10 mg of a compound described herein and 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 280, 320, 340, 360, 380, or 400 mg of an angiotensin II receptor antagonist. In certain embodiments, the dosage unit comprises 15 mg of a compound described herein and 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 280, 320, 340, 360, 380, or 400 mg of an angiotensin II receptor antagonist. In certain embodiments, the dosage unit comprises 20 mg of a compound described herein and 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 280, 320, 340, 360, 380, or 400 mg of an angiotensin II receptor antagonist. In certain embodiments, the dosage unit comprises 25 mg of a compound described herein and 20, 30, 40, 50, 60,

70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 280, 320, 340, 360, 380, or 400 mg of an angiotensin II receptor antagonist. In certain embodiments, the dosage unit comprises 30 mg of a compound described herein and 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 280, 320, 340, 360, 380, or 400 mg of an angiotensin II receptor antagonist. In certain embodiments, the dosage unit comprises 35 mg of a compound described herein and 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 280, 320, 340, 360, 380, or 400 mg of an angiotensin II receptor antagonist. In certain embodiments, the dosage unit comprises 40 mg of a compound described herein and 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 280, 320, 340, 360, 380, or 400 mg of an angiotensin II receptor antagonist. In certain embodiments, the dosage unit comprises 45 mg of a compound described herein and 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 280, 320, 340, 360, 380, or 400 mg of an angiotensin II receptor antagonist. In certain embodiments, the dosage unit comprises 50 mg of a compound described herein and 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 280, 320, 340, 360, 380, or 400 mg of an angiotensin II receptor antagonist. In certain embodiments, the dosage unit comprises 55 mg of a compound described herein and 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 280, 320, 340, 360, 380, or 400 mg of an angiotensin II receptor antagonist. In certain embodiments, the dosage unit comprises 60 mg of a compound described herein and 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 280, 320, 340, 360, 380, or 400 mg of an angiotensin II receptor antagonist. In certain embodiments, the dosage unit comprises 65 mg of a compound described herein and 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 280, 320, 340, 360, 380, or 400 mg of an angiotensin II receptor antagonist. In certain embodiments, the dosage unit comprises 70 mg of a compound described herein and 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 280, 320, 340, 360, 380, or 400 mg of an angiotensin II receptor

antagonist. In certain embodiments, the dosage unit comprises 75 mg of a compound described herein and 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 280, 320, 340, 360, 380, or 400 mg of an angiotensin II receptor antagonist. In certain embodiments, the dosage unit comprises 80 mg of a compound described herein and 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 280, 320, 340, 360, 380, or 400 mg of an angiotensin II receptor antagonist. In certain embodiments, the dosage unit comprises 85 mg of a compound described herein and 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 280, 320, 340, 360, 380, or 400 mg of an angiotensin II receptor antagonist. In certain embodiments, the dosage unit comprises 90 mg of a compound described herein and 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 280, 320, 340, 360, 380, or 400 mg of an angiotensin II receptor antagonist. In certain embodiments, the dosage unit comprises 95 mg of a compound described herein and 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 280, 320, 340, 360, 380, or 400 mg of an angiotensin II receptor antagonist. In certain embodiments, the dosage unit comprises 100 mg of a compound described herein and 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 280, 320, 340, 360, 380, or 400 mg of an angiotensin II receptor antagonist. A daily dose can include 5-100 mg (e.g., 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg) of a compound described herein and 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 280, 320, 340, 360, 380, or 400 mg of an angiotensin II receptor antagonist. In certain embodiments the angiotensin II receptor antagonist is valsartan (Diovan®). In certain embodiments the dosage unit further comprises a diuretic (e.g., hydrocholorothiazide). In certain embodiments the dosage unit and daily dose are equivalent. In various embodiments, the dosage unit is administered with food at anytime of the day, without food at anytime of the day, with food after an overnight fast (e.g., with breakfast), at bedtime after a low fat snack. In various embodiments, the dosage unit is administered once a day, twice a day, three times a day, four times a day. The dosage unit can optionally comprise other agents

such as 1, 2, 3, or more of an HMG CoA reductase inhibitor (e.g.a statin), a fibrate, niacin (including derivatives thereof), a glitazone, a calcium channel blocker, a biguanide, a CETP inhibitor, a probucol derivative and a sulfonylurea.

[00155] A dosage unit (e.g., an oral dosage unit) can include, for example, from 1 to 500 mg, 2 mg to 500 mg, 1 to 300 mg, 1 to 100 mg, 5 mg to 100 mg, 1 to 30 mg, 1 to 40 mg, 5 mg to 20 mg, 1 mg, 2 mg, 3 mg, 4mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, and 100 mg of a compound described herein and from 100 mg to 3000 mg (e.g., 100 mg, 200 mg, 250 mg, 300 mg, 400 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1250 mg, 1500 mg, 1750 mg, 2000 mg, 2250 mg, 2500 mg, 2750 mg, 3000 mg) of a biguanide (e.g., metformin). In certain embodiments, the dosage unit comprises 5 mg of a compound described herein and 100, 200, 250, 300, 400, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1250, 1500, 1750, 2000, 2250, 2500, 2750, or 3000 mg of a biguanide. In certain embodiments, the dosage unit comprises 10 mg of a compound described herein and 100, 200, 250, 300, 400, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1250, 1500, 1750, 2000, 2250, 2500, 2750, or 3000 mg of a biguanide. In certain embodiments, the dosage unit comprises 15 mg of a compound described herein and 100, 200, 250, 300, 400, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1250, 1500, 1750, 2000, 2250, 2500, 2750, or 3000 mg of a biguanide. In certain embodiments, the dosage unit comprises 20 mg of a compound described herein and 100, 200, 250, 300, 400, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1250, 1500, 1750, 2000, 2250, 2500, 2750, or 3000 mg of a biguanide. In certain embodiments, the dosage unit comprises 25 mg of a compound described herein and 100, 200, 250, 300, 400, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1250, 1500, 1750, 2000, 2250, 2500, 2750, or 3000 mg of a biguanide. In certain embodiments, the dosage unit comprises 30 mg of a compound described herein and 100, 200, 250, 300, 400, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1250, 1500, 1750, 2000, 2250, 2500, 2750, or 3000 mg of a biguanide. In certain embodiments, the dosage unit comprises 35 mg of a

compound described herein and 100, 200, 250, 300, 400, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1250, 1500, 1750, 2000, 2250, 2500, 2750, or 3000 mg of a biguanide. In certain embodiments, the dosage unit comprises 40 mg of a compound described herein and 100, 200, 250, 300, 400, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1250, 1500, 1750, 2000, 2250, 2500, 2750, or 3000 mg of a biguanide. In certain embodiments, the dosage unit comprises 45 mg of a compound described herein and 100, 200, 250, 300, 400, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1250, 1500, 1750, 2000, 2250, 2500, 2750, or 3000 mg of a biguanide. In certain embodiments, the dosage unit comprises 50 mg of a compound described herein and 100, 200, 250, 300, 400, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1250, 1500, 1750, 2000, 2250, 2500, 2750, or 3000 mg of a biguanide. In certain embodiments, the dosage unit comprises 55 mg of a compound described herein and 100, 200, 250, 300, 400, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1250, 1500, 1750, 2000, 2250, 2500, 2750, or 3000 mg of a biguanide. In certain embodiments, the dosage unit comprises 60 mg of a compound described herein and 100, 200, 250, 300, 400, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1250, 1500, 1750, 2000, 2250, 2500, 2750, or 3000 mg of a biguanide. In certain embodiments, the dosage unit comprises 65 mg of a compound described herein and 100, 200, 250, 300, 400, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1250, 1500, 1750, 2000, 2250, 2500, 2750, or 3000 mg of a biguanide. In certain embodiments, the dosage unit comprises 70 mg of a compound described herein and 100, 200, 250, 300, 400, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1250, 1500, 1750, 2000, 2250, 2500, 2750, or 3000 mg of a biguanide. In certain embodiments, the dosage unit comprises 75 mg of a compound described herein and 100, 200, 250, 300, 400, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1250, 1500, 1750, 2000, 2250, 2500, 2750, or 3000 mg of a biguanide. In certain embodiments, the dosage unit comprises 80 mg of a compound described herein and 100, 200, 250, 300, 400, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1250, 1500, 1750, 2000, 2250, 2500, 2750, or 3000 mg of a biguanide. In certain embodiments, the dosage unit comprises 85 mg of a compound described herein and 100, 200, 250, 300, 400, 500, 550, 600, 650, 700,

750, 800, 850, 900, 950, 1000, 1250, 1500, 1750, 2000, 2250, 2500, 2750, or 3000 mg of a biguanide. In certain embodiments, the dosage unit comprises 90 mg of a compound described herein and 100, 200, 250, 300, 400, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1250, 1500, 1750, 2000, 2250, 2500, 2750, or 3000 mg of a biguanide. In certain embodiments, the dosage unit comprises 95 mg of a compound described herein and 100, 200, 250, 300, 400, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1250, 1500, 1750, 2000, 2250, 2500, 2750, or 3000 mg of a biguanide. In certain embodiments, the dosage unit comprises 100 mg of a compound described herein and 100, 200, 250, 300, 400, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1250, 1500, 1750, 2000, 2250, 2500, 2750, or 3000 mg of a biguanide. A daily dose can include 5-100 mg (e.g., 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg) of a compound described herein and 100, 200, 250, 300, 400, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1250, 1500, 1750, 2000, 2250, 2500, 2750, or 3000 mg of a biguanide. In certain embodiments the biguanide is metformin (metformin hydrochloride, (Glucophage®, Glucophage® XR)). In certain embodiments the dosage unit and daily dose are equivalent. In various embodiments, the dosage unit is administered with food at anytime of the day, without food at anytime of the day, with food after an overnight fast (e.g., with breakfast), at bedtime after a low fat snack. In various embodiments, the dosage unit is administered once a day, twice a day, three times a day, four times a day. The dosage unit can optionally comprise other agents such as 1, 2, 3, or more of an HMG CoA reductase inhibitor (e.g.a statin), a fibrate, niacin (including derivatives thereof), a glitazone, a calcium channel blocker, an angiotensin II receptor antagonist, a CETP inhibitor, a probucol derivative and a sulfonylurea.

[00156] A dosage unit (e.g., an oral dosage unit) can include, for example, from 1 to 500 mg, 2 mg to 500 mg, 1 to 300 mg, 1 to 100 mg, 5 mg to 100 mg, 1 to 30 mg, 1 to 40 mg, 5 mg to 20 mg, 1 mg, 2 mg, 3 mg, 4mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, and 100 mg of a compound described herein and from 1 to 40 mg (e.g., 1 mg, 1.25 mg, 1.5 mg, 1.75 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg,

7.5 mg, 8 mg, 9 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 g) of a sulfonylurea (e.g., glipizide, glyburide). In certain embodiments, the dosage unit comprises 5 mg of a compound described herein and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, or 40 mg of a sulfonylurea. In certain embodiments, the dosage unit comprises 10 mg of a compound described herein and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, or 40 mg of a sulfonylurea. In certain embodiments, the dosage unit comprises 15 mg of a compound described herein and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, or 40 mg of a sulfonylurea. In certain embodiments, the dosage unit comprises 20 mg of a compound described herein and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, or 40 mg of a sulfonylurea. In certain embodiments, the dosage unit comprises 25 mg of a compound described herein and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, or 40 mg of a sulfonylurea. In certain embodiments, the dosage unit comprises 30 mg of a compound described herein and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, or 40 mg of a sulfonylurea. In certain embodiments, the dosage unit comprises 35 mg of a compound described herein and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, or 40 mg of a sulfonylurea. In certain embodiments, the dosage unit comprises 40 mg of a compound described herein and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, or 40 mg of a sulfonylurea. In certain embodiments, the dosage unit comprises 45 mg of a compound described herein and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, or 40 mg of a sulfonylurea. In certain embodiments, the dosage unit comprises 50 mg of a compound described herein and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, or 40 mg of a sulfonylurea. In certain embodiments, the dosage unit comprises 55 mg of a compound described herein and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, or 40 mg of a sulfonylurea. In certain embodiments, the dosage unit comprises 60 mg of a compound described herein and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, or 40 mg of a sulfonylurea. In certain embodiments, the dosage unit comprises 65 mg of a compound described herein and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, or 40 mg of a sulfonylurea. In certain embodiments,

the dosage unit comprises 70 mg of a compound described herein and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, or 40 mg of a sulfonylurea. In certain embodiments, the dosage unit comprises 75 mg of a compound described herein and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, or 40 mg of a sulfonylurea. In certain embodiments, the dosage unit comprises 80 mg of a compound described herein and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, or 40 mg of a sulfonylurea. In certain embodiments, the dosage unit comprises 85 mg of a compound described herein and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, or 40 mg of a sulfonylurea. In certain embodiments, the dosage unit comprises 90 mg of a compound described herein and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, or 40 mg of a sulfonylurea. In certain embodiments, the dosage unit comprises 95 mg of a compound described herein and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, or 40 mg of a sulfonylurea. In certain embodiments, the dosage unit comprises 100 mg of a compound described herein and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, or 40 mg of a sulfonylurea. A daily dose can include 5-100 mg (e.g., 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg) of a compound described herein and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, or 40 mg of a sulfonylurea. In certain embodiments the sulfonylurea is glipizide (Glucotrol® Glucotrol XL®). In certain embodiments the sulfonylurea is glyburide (Micronase®, Glynase Prestab®, Diabeta®). In certain embodiments the dosage unit and daily dose are equivalent. In various embodiments, the dosage unit is administered with food at anytime of the day, without food at anytime of the day, with food after an overnight fast (e.g., with breakfast), at bedtime after a low fat snack. In various embodiments, the dosage unit is administered once a day, twice a day, three times a day, four times a day. The dosage unit can optionally comprise other agents such as 1, 2, 3, or more of an HMG CoA reductase inhibitor (e.g.a statin), a fibrate, niacin (including derivatives thereof), a glitazone, a calcium channel blocker, an angiotensin II receptor antagonist, a CETP inhibitor, a probucol derivative and a biguanide.

[00157] A dosage unit (e.g., an oral dosage unit) can include, for example, from 1 to 500 mg, 2 mg to 500 mg, 1 to 300 mg, 1 to 100 mg, 5 mg to 100 mg, 1 to 30 mg, 1 to

40 mg, 5 mg to 20 mg, 1 mg, 2 mg, 3 mg, 4mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, and 100 mg of a compound described herein and from 10 to 1800 mg (e.g., 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg) of a CETP inhibitor. In certain embodiments, the dosage unit comprises 5 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, or 1800 mg of a CETP inhibitor. In certain embodiments, the dosage unit comprises 10 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, or 1800 mg of a CETP inhibitor. In certain embodiments, the dosage unit comprises 15 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, or 1800 mg of a CETP inhibitor. In certain embodiments, the dosage unit comprises 20 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, or 1800 mg of a CETP inhibitor. In certain

embodiments, the dosage unit comprises 25 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, or 1800 mg of a CETP inhibitor. In certain embodiments, the dosage unit comprises 30 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, or 1800 mg of a CETP inhibitor. In certain embodiments, the dosage unit comprises 35 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, or 1800 mg of a CETP inhibitor. In certain embodiments, the dosage unit comprises 40 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, or 1800 mg of a CETP inhibitor t. In certain embodiments, the dosage unit comprises 45 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, or 1800 mg of a CETP inhibitor. In certain embodiments, the dosage unit comprises 50 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450

mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, or 1800 mg of a CETP inhibitor. In certain embodiments, the dosage unit comprises 55 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, or 1800 mg of a CETP inhibitor. In certain embodiments, the dosage unit comprises 60 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, or 1800 mg of a CETP inhibitor. In certain embodiments, the dosage unit comprises 65 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, or 1800 mg of a CETP inhibitor. In certain embodiments, the dosage unit comprises 70 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, or 1800 mg of a CETP inhibitor. In certain embodiments, the dosage unit comprises 75 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, or 1800 mg of a CETP inhibitor. In certain embodiments, the dosage unit

comprises 80 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, or 1800 mg of a CETP inhibitor. In certain embodiments, the dosage unit comprises 85 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, or 1800 mg of a CETP inhibitor. In certain embodiments, the dosage unit comprises 90 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, or 1800 mg of a CETP inhibitor. In certain embodiments, the dosage unit comprises 95 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, or 1800 mg of a CETP inhibitor. In certain embodiments, the dosage unit comprises 100 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, or 1800 mg of a CETP inhibitor. A daily dose can include 5-100 mg (e.g., 5, 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg) of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 200 mg, 250 mg,

300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, or 1800 mg of a CETP inhibitor. In certain embodiments the CETP inhibitor is torcetrapib. In certain embodiments the dosage unit includes 5-100 mg (e.g., 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg) of a compound described herein and 30 mg, 60 mg, 90 mg, 100 mg, or 120 mg of torcetrapib. In certain embodiments the CETP inhibitor is JTT-705. In certain embodiments the dosage unit includes 5-100 mg (e.g., 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg) of a compound described herein and 100 mg, 300 mg, 600 mg, 900 mg, or 1800 mg of JTT-705. In certain embodiments the dosage unit further comprises a diuretic (e.g., hydrocholorothiazide). In certain embodiments the dosage unit and daily dose are equivalent. In various embodiments, the dosage unit is administered with food at anytime of the day, without food at anytime of the day, with food after an overnight fast (e.g., with breakfast), at bedtime after a low fat snack. In various embodiments, the dosage unit is administered once a day, twice a day, three times a day, four times a day. The dosage unit can optionally comprise other agents such as 1, 2, 3, or more of an HMG CoA reductase inhibitor (e.g.a statin), a fibrate, niacin (including derivatives thereof), a glitazone, a calcium channel blocker, a biguanide, an angiotensin II receptor antagonist and a sulfonylurea.

[00158] A dosage unit (e.g., an oral dosage unit) can include, for example, from 1 to 500 mg, 2 mg to 500 mg, 1 to 300 mg, 1 to 100 mg, 5 mg to 100 mg, 1 to 30 mg, 1 to 40 mg, 5 mg to 20 mg, 1 mg, 2 mg, 3 mg, 4mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, and 100 mg of a compound described herein and from 10 to 1000 mg (e.g., 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg) of a Probucol derivative. In certain

embodiments, the dosage unit comprises 5 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of a Probucol derivative. In certain embodiments, the dosage unit comprises 10 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of a Probucol derivative. In certain embodiments, the dosage unit comprises 15 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of a Probucol derivative. In certain embodiments, the dosage unit comprises 20 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of a Probucol derivative. In certain embodiments, the dosage unit comprises 25 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of a Probucol derivative. In certain embodiments, the dosage unit comprises 30 mg of a compound described herein and

10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of a Probucol derivative. In certain embodiments, the dosage unit comprises 35 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of a Probucol derivative. In certain embodiments, the dosage unit comprises 40 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of a Probucol derivative. In certain embodiments, the dosage unit comprises 45 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of a Probucol derivative. In certain embodiments, the dosage unit comprises 50 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of a Probucol derivative. In certain embodiments, the dosage unit comprises 55 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg,

120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of a Probucol derivative. In certain embodiments, the dosage unit comprises 60 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of a Probucol derivative. In certain embodiments, the dosage unit comprises 65 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of a Probucol derivative. In certain embodiments, the dosage unit comprises 70 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of a Probucol derivative. In certain embodiments, the dosage unit comprises 75 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of a Probucol derivative. In certain embodiments, the dosage unit comprises 80 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210

mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of a Probucol derivative. In certain embodiments, the dosage unit comprises 85 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of a Probucol derivative. In certain embodiments, the dosage unit comprises 90 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of a Probucol derivative. In certain embodiments, the dosage unit comprises 95 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of a Probucol derivative. In certain embodiments, the dosage unit comprises 100 mg of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of a Probucol derivative. A daily dose can include 5-100 mg (e.g., 5, 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg) of a compound described herein and 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg,

250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of a Probucol derivative. In certain embodiments the Probucol derivative is AGI-1067. In certain embodiments the dosage unit includes 5-100 mg (e.g., 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg) of a compound described herein and 70 mg, 140 mg, 280 mg, or 300 mg of AGI-1067. In certain embodiments the dosage unit further comprises a diuretic (e.g., hydrocholorothiazide). In certain embodiments the dosage unit and daily dose are equivalent. In various embodiments, the dosage unit is administered with food at anytime of the day, without food at anytime of the day, with food after an overnight fast (e.g., with breakfast), at bedtime after a low fat snack. In various embodiments, the dosage unit is administered once a day, twice a day, three times a day, four times a day. The dosage unit can optionally comprise other agents such as 1, 2, 3, or more of an HMG CoA reductase inhibitor (e.g.a statin), a fibrate, niacin (including derivatives thereof), a glitazone, a calcium channel blocker, a biguanide, an angiotensin II receptor antagonist and a sulfonylurea.

[00159] It can be useful to administer a compound described herein together with a sterol or stanol composition. Sterols and stanols include but are not limited to those described herein. Plant sterols and stanols (e.g., beta-sitosterol) have been used as dietary supplements to reduce serum cholesterol levels. Plant sterol can be esterified to create stanol esters (also referred to as stanols), which are also used as food additives. Sterols are typically derived from agricultural sources, such as corn, soy-based, and pine tree mixtures. Stanols can be created through the reaction of the sterol with the suitable acid. Suitable acids include saturated, unsaturated, and polyunsaturated acids. Suitable acids include but are not limited to, stearic, butyric, lauric, palmitic, oleic, linoleic, linolenic, docohexanoic acid, and the like. Suitable methods for preparing these esters are well known in the art, see, e.g., US5502045 and US5723747. Sterols and sterol esters can be formulated a self-dispersing particles that are small enough to be effective when administered by ingestion (see, e.g., US6387411, US6376481 and US20040033202). Sterols and/or sterol esters in particle form can be combined with a compound described herein to create useful

pharameutical compositons which can also include other agents such as 1, 2, 3, or more of an HMG-CoA reductase inhibitor (e.g., a statin such as atorvastatin, atorvastatin calcium, rosuvastatin, rosuvastatin calcium, simvastatin), a fibrate (e.g., fenofibrate(Tricor®)), niacin (including derivatives and extended release formulations (e.g., Niaspan®) thereof), a glitazone (e.g., rosiglitazone maleate (Avandia®), piogilitazone hydrochloride(Actos®)), a calcium channel blocker (e.g., amlodipine besylate (Norvasc®)), an angiotensin II receptor antagonist (e.g., valsartan (Diovan®, Diovan HCT® (valsartan and hydrochlorothiazide))), a biguanide (e.g., metformin (Glucophage®)), a sulfonylurea (e.g., glipizide (Glucotrol®, Glucotrol XL®), glyburide (Micronase®, Glynase Prestab®, Diabeta®), and Glucovance® (glyburide and metformin). The pharmaceutical composition can include additional ingredients such as stabilizers or bulking agents. The sterol particles in the composition can have any suitable size, e.g., 10-150 microns in diameter. However, to improve absorption in the body it can be desirable to use much smaller particles, e.g., less than 2000 nm in diameter as explained in US20040033202. Thus, pharmaceutical compositions that include a compound described herein can include sterol nanoparticles, such as sitosterol and/or phytosterol nanoparticles, which have an effective average particle size of less than about 2000 nm, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods. The particles can be created by methods which include: milling, precipitation and homogenization. For example, homogenization methods are described in US5510118. The method includes dispersing sterol particles in a liquid dispersion medium in which the sterol is poorly soluble, followed by subjecting the dispersion to homogenization to reduce the particle size of the sterol to the desired effective average particle size. The sterol particles are preferably reduced in size in the

presence of at least one surface stabilizer. Alternatively, the sterol particles can be contacted with one or more surface stabilizers either before or after attrition. Other compounds, such as a diluent, can be added to the sterol/surface stabilizer composition before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode. Surface stabilizers can be used in the formulations. Suitable surface stabilizers include: cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucop- yranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β-D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

[00160] It can be useful to administer a compound described herein together with a polycosanol composition. Polycosanol compositions are complex mixtures of concentrated n-alkyl alcohols derived from, e.g., sugar cane and the wax of honey

bees. Polycosanol compositions are reported to produce cholesterol lowering effects within the first 6-8 weeks of use. According to US20030232796, at a daily polycosanol dosage of 10 mg taken at night, LDL cholesterol levels typically drop by 20-25% within the first six months of use. At a dosage of 20 mg, LDL levels typically drop by 25-30%. HDL levels typically increase by 15-25% only after two months of use. The combined LDL reduction and HDL increase will produce a significant and dramatic improvement in the LDL to HDL ratio. Polycosanol can include fatty acid components including: 1-Octacosanol, 1-Triacontanol, 1-Tetracosanol, 1-Heptacosanol, and 1-Hexacosanol. Typical usage levels range from 500-10,000 micrograms per serving/dose. Typical commercially available commercial compositions are 90% minimum fatty alcohols of (a) 1-Tetracosanol: 0-10%; (b) 1-Hexacosanol: 2-15%; (c) 1-Heptacosanol: 0-0.5%; (d) 1-Octacosanol: 55-70%; (e) 1-Nonacosanol: 0-10%; (f) 1-Triacontanol: 5-20%; (g) 1-Dotriacontanol: 0.1-10%; and (h) 1-Tetratriacontanol: 0.1-10%. Polycosanol compositions can be formulated as described above for stanols both with respect to particle size and overall formulation. They can also be formulated according to the disclosures provided in WO05067903. In addition to the compounds described herein, the formulation can include other agents such as 1, 2, 3, or more of an HMG-CoA reductase inhibitor (e.g., a statin such as atorvastatin, atorvastatin calcium, rosuvastatin, rosuvastatin calcium, simvastatin), a fibrate (e.g., fenofibrate(Tricor®)), niacin (including derivatives and extended release formulations (e.g., Niaspan®) thereof), a glitazone (e.g., rosiglitazone maleate (Avandia®), piogilitazone hydrochloride(Actos®)), a calcium channel blocker (e.g., amlodipine besylate (Norvasc®)), an angiotensin II receptor antagonist (e.g., valsartan (Diovan®, Diovan HCT® (valsartan and hydrochlorothiazide))), a biguanide (e.g., metformin (Glucophage®)), a sulfonylurea (e.g., glipizide (Glucotrol®, Glucotrol XL®), glyburide (Micronase®, Glynase Prestab®, Diabeta®), and Glucovance® (glyburide and metformin).

[00161] Combining two or more active ingredients in single dosage form results in the possibility of chemical interactions between the active drug substances. For example, acidic and basic active ingredients can react with each other and acidic active ingredients can facilitate the degradation of acid labile substances. Thus, in

certain dosage forms, acidic and basic substances can be physically separated as two distinct or isolated layers in a compressed tablet, or in the core and shell of a press-coated tablet. Additional agents that are compatible with acidic as well as basic substances, have the flexibility of being placed in either layer. In certain multiple layer compositions at least one active ingredient can be enteric-coated. In certain embodiments thereof at least one active ingredient can be presented in a controlled release form. In certain embodiments where a combination of three or more active substances are used, they can be presented as physically isolated segments of a compressed mutlilayer tablet, which can be optionally film coated.

[00162] The therapeutic combinations described herein can be formulated as a tablet or capsule comprising a plurality of beads, granules, or pellets. All active ingredients including the vitamins of the combination are formulated into granules or beads or pellets that are further coated with a protective coat, an enteric coat, or a film coat to avoid the possible chemical interactions. Granulation and coating of granules or beads is done using techniques well known to a person skilled in the art. At least one active ingredient can present in a controlled release form. Finally these coated granules or beads are filled into hard gelatin capsules or compressed to form tablets.

[00163] The therapeutic combinations described herein can be formulated as a capsule comprising microtablets or minitablets of all active ingredients. Microtablets of the individual agents can be prepared using well known pharmaceutical procedures of tablet making like direct compression, dry granulation or wet granulation. Individual microtablets can be filled into hard gelatin capsules. A final dosage form may comprise one or more microtablets of each individual component. The microtablets may be film coated or enteric coated.

[00164] The therapeutic combinations described herein can be formulated as a capsule comprising one or more microtablets and powder, or one or more microtablets and granules or beads. In order to avoid interactions between drugs, some active ingredients of a said combination can be formulated as microtablets and the others filled into capsules as a powder, granules, or beads. The microtablets may be film coated or enteric coated. At least one active ingredient can be presented in controlled release form.

[00165] The therapeutic combinations described herein can be formulated wherein the active ingredients are distributed in the inner and outer phase of tablets. In an attempt to divide chemically incompatible components of proposed combination, few interacting components are converted in granules or beads using well known pharmaceutical procedures in prior art. The prepared granules or beads (inner phase) are then mixed with outer phase comprising the remaining active ingredients and at least one pharmaceutically acceptable excipient. The mixture thus comprising inner and outer phase is compressed into tablets or molded into tablets. The granules or beads can be controlled release or immediate release beads or granules, and can further be coated using an enteric polymer in an aqueous or non-aqueous system, using methods and materials that are known in the art.

[00166] The therapeutic combinations described herein can be formulated as single dosage unit comprising suitable buffering agent. All powdered ingredients of said combination are mixed and a suitable quantity of one or more buffering agents is added to the blend to minimize possible interactions.

[00167] The agents described herein, alone or in combination, can be combined with any pharmaceutically acceptable carrier or medium. Thus, they can be combined with materials that do not produce an adverse, allergic or otherwise unwanted reaction when administered to a patient. The carriers or mediums used can include solvents, dispersants, coatings, absorption promoting agents, controlled release agents, and one or more inert excipients (which include starches, polyols, granulating agents, microcrystalline cellulose, diluents, lubricants, binders, disintegrating agents, and the like), etc. If desired, tablet dosages of the disclosed compositions may be coated by standard aqueous or nonaqueous techniques. The agents described herein, alone or in combination, can be formulated using Nanocrystal® technology (Elan Corporation, Dublin, Ireland).

[00168] The agents can be a free acid or base, or a pharmacologically acceptable salt thereof. Solids can be dissolved or dispersed immediately prior to administration or earlier. In some circumstances the preparations include a preservative to prevent the growth of microorganisms. The pharmaceutical forms suitable for injection can include sterile aqueous or organic solutions or dispersions which include, e.g., water,

an alcohol, an organic solvent, an oil or other solvent or dispersant (e.g., glycerol, propylene glycol, polyethylene glycol, and vegetable oils). The formulations may contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. Pharmaceutical agents can be sterilized by filter sterilization or by other suitable means

[00169] Suitable pharmaceutical compositions in accordance with the invention will generally include an amount of the active compound(s) with an acceptable pharmaceutical diluent or excipient, such as a sterile aqueous solution, to give a range of final concentrations, depending on the intended use. The techniques of preparation are generally well known in the art, as exemplified by Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Company, 1995.

[00170] The agent can be in the form of a pharmaceutically acceptable salt. Such salts are prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Examples of salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. In some embodiments, the salt can be an ammonium, calcium, magnesium, potassium, or sodium salt. Examples of salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, benethamine, *N,N'*-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, diethanolamine, ethanolamine, ethylenediamine, *N*-ethylmorpholine, *N*-ethylpiperidine, epolamine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, meglumine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, and trolamine, tromethamine. Examples of other salts include tris, arecoline, arginine, barium, betaine, bismuth, chloroprocaine, choline, clemizole, deanol, imidazole, and morpholineethanol.

[00171] The agents of the invention can be administered orally, e.g., as a tablet or cachet containing a predetermined amount of the active ingredient, pellet, gel, paste,

syrup, bolus, electuary, slurry, capsule; powder; granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion, via a liposomal formulation (see, e.g., EP736299) or in some other form. Orally administered compositions can include binders, lubricants, inert diluents, lubricating, surface active or dispersing agents, flavoring agents, and humectants. Orally administered formulations such as tablets may optionally be coated or scored and may be formulated so as to provide sustained, delayed or controlled release of the active ingredient therein. The agents of the invention can also be administered by captisol delivery technology, rectal suppository or parenterally.

[00172] The agents described herein can be either in their free form or as a salt can be combined with a polymer such as polylactic-glycoloic acid (PLGA), poly-(I)-lactic-glycolic-tartaric acid (P(I)LGT) (WO01/12233), polyglycolic acid (US3773919), polylactic acid (US4767628), poly(M-caprolactone) and poly(alkylene oxide) (US20030068384) to create a sustained release formulation. Such formulations can be used within implants that release a compound of the invention and/or another agent over a period of a few days, a few weeks or several months depending on the polymer, the particle size of the polymer, and the size of the implant (see, e.g., US6620422 and WO05/011769). Other sustained release formulations are described in EP0467389, WO93/241150, US5612052, WO97/40085, WO03/075887, WO01/01964, US5922356, WO94/155587, WO02/074247, WO98/25642, US5968895, US6180608, US20030171296, US20020176841, US5672659, US5893985, US5134122, US5192741, US5192741, US4668506, US4713244, US5445832 US4931279, US5980945, WO02/058672, WO9726015, WO97/04744, and US20020019446. In such sustained release formulations microparticles of compound are combined with microparticles of polymer. US6011011 and WO94/06452 described a sustained release formulation providing either polyethylene glycols (e.g., PEG 300 and PEG 400) or triacetin. WO03/053401 describes a formulation which may both enhance bioavailability and provide controlled release of the agent within the GI tract. Additional controlled release formulations are described in WO02/38129, EP326151, US5236704, WO02/30398, WO98/13029, US20030064105, US20030138488,

US20030216307, US6667060, WO01/49249, WO01/49311, WO01/49249, WO01/49311, US5877224, WO05/030179, WO05/027878, WO05/012488 and WO05/007074.

Controlled release formulations

[00173] In general, one can provide for controlled release of the agents described herein through the use of a wide variety of polymeric carriers and controlled release systems including erodible and non-erodible matrices, osmotic control devices, various reservoir devices, enteric coatings and multiparticulate control devices.

[00174] Matrix devices are a common device for controlling the release of various agents. In such devices, the agents described herein are generally present as a dispersion within the polymer matrix, and are typically formed by the compression of a polymer/drug mixture or by dissolution or melting. The dosage release properties of these devices may be dependent upon the solubility of the agent in the polymer matrix or, in the case of porous matrices, the solubility in the sink solution within the pore network, and the tortuosity of the network. In one instance, when utilizing an erodible polymeric matrix, the matrix imbibes water and forms an aqueous-swollen gel that entraps the agent. The matrix then gradually erodes, swells, disintegrates or dissolves in the GI tract, thereby controlling release of one or more of the agents described herein. In non-erodible devices, the agent is released by diffusion through an inert matrix.

[00175] Agents described herein can be incorporated into an erodible or non-erodible polymeric matrix controlled release device. By an erodible matrix is meant aqueous-erodible or water-swellable or aqueous-soluble in the sense of being either erodible or swellable or dissolvable in pure water or requiring the presence of an acid or base to ionize the polymeric matrix sufficiently to cause erosion or dissolution. When contacted with the aqueous environment of use, the erodible polymeric matrix imbibes water and forms an aqueous-swollen gel or matrix that entraps the agent described herein. The aqueous-swollen matrix gradually erodes, swells, disintegrates or dissolves in the environment of use, thereby controlling the release of a compound

described herein to the environment of use. Nonlimiting examples of such devices are disclosed in U. S. Patent Application Serial No. 09/495,059 filed January 31, 2000.

[00176] The erodible polymeric matrix into which an agent described herein can be incorporated may generally be described as a set of excipients that are mixed with the agent following its formation that, when contacted with the aqueous environment of use imbibes water and forms a water-swollen gel or matrix that entraps the drug form. Drug release may occur by a variety of mechanisms, for example, the matrix may disintegrate or dissolve from around particles or granules of the agent or the agent may dissolve in the imbibed aqueous solution and diffuse from the tablet, beads or granules of the device. One ingredient of this water-swollen matrix is the water-swellable, erodible, or soluble polymer, which may generally be described as an osmopolymer, hydrogel or water-swellable polymer. Such polymers may be linear, branched, or crosslinked. The polymers may be homopolymers or copolymers. In certain embodiments, they may be synthetic polymers derived from vinyl, acrylate, methacrylate, urethane, ester and oxide monomers. In other embodiments, they can be derivatives of naturally occurring polymers such as polysaccharides (e.g., chitin, chitosan, dextran and pullulan; gum agar, gum arabic, gum karaya, locust bean gum, gum tragacanth, carrageenans, gum ghatti, guar gum, xanthan gum and scleroglucan), starches (e.g., dextrin and maltodextrin), hydrophilic colloids (e.g., pectin), phosphatides (e.g., lecithin), alginates (e.g., ammonium alginate, sodium, potassium or calcium alginate, propylene glycol alginate), gelatin, collagen, and cellulosics. Cellulosics are cellulose polymer that has been modified by reaction of at least a portion of the hydroxyl groups on the saccharide repeat units with a compound to form an ester-linked or an ether-linked substituent. For example, the cellulosic ethyl cellulose has an ether linked ethyl substituent attached to the saccharide repeat unit, while the cellulosic cellulose acetate has an ester linked acetate substituent. In certain embodiments, the cellulosics for the erodible matrix comprises aqueous-soluble and aqueous-erodible cellulosics can include, for example, ethyl cellulose (EC), methylethyl cellulose (MEC), carboxymethyl cellulose (CMC), CMEC, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), cellulose acetate (CA), cellulose propionate (CP), cellulose butyrate (CB), cellulose acetate butyrate (CAB), CAP,

CAT, hydroxypropyl methyl cellulose (HPMC), HPMCP, HPMCAS, hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), and ethylhydroxy ethylcellulose (EHEC). In certain embodiments, the cellulosics comprises various grades of low viscosity (MW less than or equal to 50,000 daltons, for example, the Dow Methocel™ series E5, E15LV, E50LV and K100LY) and high viscosity (MW greater than 50,000 daltons, for example, E4MCR, E10MCR, K4M, K15M and K100M and the Methocel™ K series) HPMC. Other commercially available types of HPMC include the Shin Etsu Metolose 90SH series.

[00177] The choice of matrix material can have a large effect on the maximum drug concentration attained by the device as well as the maintenance of a high drug concentration. The matrix material can be a concentration-enhancing polymer, for example, as described in WO05/011634.

[00178] Other materials useful as the erodible matrix material include, but are not limited to, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, glycerol fatty acid esters, polyacrylamide, polyacrylic acid, copolymers of ethacrylic acid or methacrylic acid (EUDRAGITO, Rohm America, Inc., Piscataway, New Jersey) and other acrylic acid derivatives such as homopolymers and copolymers of butylmethacrylate, methylmethacrylate, ethylmethacrylate, ethylacrylate, (2-dimethylaminoethyl) methacrylate, and (trimethylaminoethyl) methacrylate chloride.

[00179] The erodible matrix polymer may contain a wide variety of the same types of additives and excipients known in the pharmaceutical arts, including osmopolymers, osmagens, solubility-enhancing or-retarding agents and excipients that promote stability or processing of the device.

[00180] Alternatively, the agents of the present invention may be administered by or incorporated into a non-erodible matrix device. In such devices, an agent described herein is distributed in an inert matrix. The agent is released by diffusion through the inert matrix. Examples of materials suitable for the inert matrix include insoluble plastics (e.g methyl acrylate-methyl methacrylate copolymers, polyvinyl chloride, polyethylene), hydrophilic polymers (e.g., ethyl cellulose, cellulose acetate, crosslinked polyvinylpyrrolidone (also known as crospovidone)), and fatty compounds (e.g., carnauba wax, microcrystalline wax, and triglycerides). Such devices are

described further in Remington: The Science and Practice of Pharmacy, 20th edition (2000).

[00181] Matrix controlled release devices may be prepared by blending an agent described herein and other excipients together, and then forming the blend into a tablet, caplet, pill, or other device formed by compressive forces. Such compressed devices may be formed using any of a wide variety of presses used in the fabrication of pharmaceutical devices. Examples include single-punch presses, rotary tablet presses, and multilayer rotary tablet presses, all well known in the art. See for example, Remington: The Science and Practice of Pharmacy, 20th Edition, 2000. The compressed device may be of any shape, including round, oval, oblong, cylindrical, or triangular. The upper and lower surfaces of the compressed device may be flat, round, concave, or convex.

[00182] In certain embodiments, when formed by compression, the device has a strength of at least 5 Kiloponds (Kp)/cm^2 (for example, at least 7 Kp/cm^2). Strength is the fracture force, also known as the tablet hardness required to fracture a tablet formed from the materials, divided by the maximum cross-sectional area of the tablet normal to that force. The fracture force may be measured using a Schleuniger Tablet Hardness Tester, Model 6D. The compression force required to achieve this strength will depend on the size of the tablet, but generally will be greater than about 5 kP/cm^2. Friability is a well-know measure of a device's resistance to surface abrasion that measures weight loss in percentage after subjecting the device to a standardized agitation procedure. Friability values of from 0.8 to 1.0% are regarded as constituting the upper limit of acceptability. Devices having a strength of greater than 5 kP/cm^2 generally are very robust, having a friability of less than 0. 5%. Other methods for forming matrix controlled-release devices are well known in the pharmaceutical arts. See for example, Remington: The Science and Practice of Pharmacy, 20th Edition, 2000.

[00183] As noted above, the agents described herein may also be incorporated into an osmotic control device. Such devices generally include a core containing one or more agents as described herein and a water permeable, non-dissolving and non-eroding coating surrounding the core which controls the influx of water into the core

from an aqueous environment of use so as to cause drug release by extrusion of some or all of the core to the environment of use. In certain embodiments, the coating is polymeric, aqueous-permeable, and has at least one delivery port. The core of the osmotic device optionally includes an osmotic agent which acts to imbibe water from the surrounding environment via such a semi-permeable membrane. The osmotic agent contained in the core of this device may be an aqueous-swellable hydrophilic polymer or it may be an osmogen, also known as an osmagent. Pressure is generated within the device which forces the agent(s) out of the device via an orifice (of a size designed to minimize solute diffusion while preventing the build-up of a hydrostatic pressure head). Nonlimiting examples of osmotic control devices are disclosed in U. S. Patent Application Serial No. 09/495,061.

[00184] Osmotic agents create a driving force for transport of water from the environment of use into the core of the device. Osmotic agents include but are not limited to water- swellable hydrophilic polymers, and osmogens (or osmagens). Thus, the core may include water-swellable hydrophilic polymers, both ionic and nonionic, often referred to as osmopolymers and hydrogels. The amount of water-swellable hydrophilic polymers present in the core may range from about 5 to about 80 wt% (including for example, 10 to 50 wt%). Nonlimiting examples of core materials include hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium alginate, polyethylene oxide (PEO), polyethylene glycol (PEG), polypropylene glycol (PPG), poly (2-hydroxyethyl methacrylate), poly (acrylic) acid, poly (methacrylic) acid, polyvinylpyrrolidone (PVP) and crosslinked PVP, polyvinyl alcohol (PVA), PVA/PVP copolymers and PVA/PVP copolymers with hydrophobic monomers such as methyl methacrylate, vinyl acetate, and the like, hydrophilic polyurethanes containing large PEO blocks, sodium croscarmellose, carrageenan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and carboxyethyl cellulose (CEC), sodium alginate, polycarbophil, gelatin, xanthan gum, and sodium starch glycolat. Other materials include hydrogels comprising interpenetrating networks of polymers that may be formed by addition or by condensation polymerization, the components of which may comprise hydrophilic and hydrophobic monomers such as those just

mentioned. Water-swellable hydrophilic polymers include but are not limited to PEO, PEG, PVP, sodium croscarmellose, HPMC, sodium starch glycolate, polyacrylic acid and crosslinked versions or mixtures thereof.

[00185] The core may also include an osmogen (or osmagent). The amount of osmogen present in the core may range from about 2 to about 70 wt% (including, for example, from 10 to 50 wt%). Typical classes of suitable osmogens are water-soluble organic acids, salts and sugars that are capable of imbibing water to thereby effect an osmotic pressure gradient across the barrier of the surrounding coating. Typical useful osmogens include but are not limited to magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, sodium sulfate, mannitol, xylitol, urea, sorbitol, inositol, raffinose, sucrose, glucose, fructose, lactose, citric acid, succinic acid, tartaric acid, and mixtures thereof. In certain embodiments, the osmogen is glucose, lactose, sucrose, mannitol, xylitol, sodium chloride, including combinations thereof.

[00186] The core may include a wide variety of additives and excipients that enhance the performance of the dosage form or that promote stability, tableting or processing. Such additives and excipients include tableting aids, surfactants, water-soluble polymers, pH modifiers, fillers, binders, pigments, disintegrants, antioxidants, lubricants and flavorants. Nonlimiting examples of additives and excipients include but are not limited to those described elsewhere herein as well as microcrystalline cellulose, metallic salts of acids (e.g., aluminum stearate, calcium stearate, magnesium stearate, sodium stearate, zinc stearate), pH control agents (e.g., buffers, organic acids, organic acid salts, organic and inorganic bases), fatty acids, hydrocarbons and fatty alcohols (e.g., stearic acid, palmitic acid, liquid paraffin, stearyl alcohol, and palmitol), fatty acid esters (e.g., glyceryl (mono-and di-) stearates, triglycerides, glyceryl (palmiticstearic) ester, sorbitan esters (e.g., sorbitan monostearate, saccharose monostearate, saccharose monopalmitate, sodium stearyl fumarate), polyoxyethylene sorbitan esters), surfactants (e.g., alkyl sulfates (e.g., sodium lauryl sulfate, magnesium lauryl sulfate), polymers (e.g., polyethylene glycols, polyoxyethylene glycols, polyoxyethylene, polyoxypropylene ethers, including copolymers thereof),

polytetrafluoroethylene), and inorganic materials (e.g., talc, calcium phosphate), cyclodextrins, sugars (e.g., lactose, xylitol), sodium starch glycolate). Nonlimiting examples of disintegrants are sodium starch glycolate (e. g., Explotab™ CLV, (microcrystalline cellulose (e. g., Avicel™), microcrystalline silicified cellulose (e.g., ProSolv™), croscarmellose sodium (e. g., Ac-Di-Sol™). When the agent described herein is a solid amorphous dispersion formed by a solvent process, such additives may be added directly to the spray-drying solution when forming an agent described herein/concentration-enhancing polymer dispersion such that the additive is dissolved or suspended in the solution as a slurry, Alternatively, such additives may be added following the spray-drying process to aid in forming the final controlled release device.

[00187] A nonlimiting example of an osmotic device consists of one or more drug layers containing an agent described herein, such as a solid amorphous drug/polymer dispersion, and a sweller layer that comprises a water-swellable polymer, with a coating surrounding the drug layer and sweller layer. Each layer may contain other excipients such as tableting aids, osmagents, surfactants, water-soluble polymers and water-swellable polymers.

[00188] Such osmotic delivery devices may be fabricated in various geometries including bilayer (wherein the core comprises a drug layer and a sweller layer adjacent to each other), trilayer (wherein the core comprises a sweller layer sandwiched between two drug layers) and concentric (wherein the core comprises a central sweller agent surrounded by the drug layer). The coating of such a tablet comprises a membrane permeable to water but substantially impermeable to drug and excipients contained within. The coating contains one or more exit passageways or ports in communication with the drug-containing layer(s) for delivering the drug agent. The drug-containing layer(s) of the core contains the drug agent (including optional osmagents and hydrophilic water-soluble polymers), while the sweller layer consists of an expandable hydrogel, with or without additional osmotic agents.

[00189] When placed in an aqueous medium, the tablet imbibes water through the membrane, causing the agent to form a dispensable aqueous agent, and causing the hydrogel layer to expand and push against the drug-containing agent, forcing the agent

out of the exit passageway. The agent can swell, aiding in forcing the drug out of the passageway. Drug can be delivered from this type of delivery system either dissolved or dispersed in the agent that is expelled from the exit passageway.

[00190] The rate of drug delivery is controlled by such factors as the permeability and thickness of the coating, the osmotic pressure of the drug-containing layer, the degree of hydrophilicity of the hydrogel layer, and the surface area of the device. Those skilled in the art will appreciate that increasing the thickness of the coating will reduce the release rate, while any of the following will increase the release rate: increasing the permeability of the coating; increasing the hydrophilicity of the hydrogel layer; increasing the osmotic pressure of the drug-containing layer; or increasing the device's surface area.

[00191] Other materials useful in forming the drug-containing agent, in addition to the agent described herein itself, include HPMC, PEO and PVP and other pharmaceutically acceptable carriers. In addition, osmagents such as sugars or salts, including but not limited to sucrose, lactose, xylitol, mannitol, or sodium chloride, may be added. Materials which are useful for forming the hydrogel layer include sodium CMC, PEO (e.g., polymers having an average molecular weight from about 5,000,000 to about 7,500,000 daltons), poly (acrylic acid), sodium (polyacrylate), sodium croscarmellose, sodium starch glycolat, PVP, crosslinked PVP, and other high molecular weight hydrophilic materials.

[00192] In the case of a bilayer geometry, the delivery port(s) or exit passageway(s) may be located on the side of the tablet containing the drug agent or may be on both sides of the tablet or even on the edge of the tablet so as to connect both the drug layer and the sweller layer with the exterior of the device. The exit passageway(s) may be produced by mechanical means or by laser drilling, or by creating a difficult-to-coat region on the tablet by use of special tooling during tablet compression or by other means.

[00193] The osmotic device can also be made with a homogeneous core surrounded by a semipermeable membrane coating, as in US3845770. The agent described herein can be incorporated into a tablet core and a semipermeable membrane coating can be applied via conventional tablet-coating techniques such as using a pan coater. A drug

delivery passageway can then be formed in this coating by drilling a hole in the coating, either by use of a laser or mechanical means. Alternatively, the passageway may be formed by rupturing a portion of the coating or by creating a region on the tablet that is difficult to coat, as described above. In one embodiment, an osmotic device comprises: (a) a single-layer compressed core comprising: (i) an agent described herein, (ii) a hydroxyethylcellulose, and (iii) an osmagent, wherein the hydroxyethylcellulose is present in the core from about 2.0% to about 35% by weight and the osmagent is present from about 15% to about 70% by weight; (b) a water-permeable layer surrounding the core; and (c) at least one passageway within the water-permeable layer (b) for delivering the drug to a fluid environment surrounding the tablet. In certain embodiments, the device is shaped such that the surface area to volume ratio (of a water-swollen tablet) is greater than 0.6 mm^{-1} (including, for example, greater than 1.0 mm^{-1}). The passageway connecting the core with the fluid environment can be situated along the tablet band area. In certain embodiments, the shape is an oblong shape where the ratio of the tablet tooling axes, i.e., the major and minor axes which define the shape of the tablet, are between 1.3 and 3 (including, for example, between 1.5 and 2.5). In one embodiment, the combination of the agent described herein and the osmagent have an average ductility from about 100 to about 200 Mpa, an average tensile strength from about 0.8 to about 2.0 Mpa, and an average brittle fracture index less than about 0.2. The single-layer core may optionally include a disintegrant, a bioavailability enhancing additive, and/or a pharmaceutically acceptable excipient, carrier or diluent. Nonlimiting examples of such devices are disclosed, for example, in U. S. provisional Patent Application Serial No. 60/353,151.

[00194] In certain embodiments, entrainment of particles of agents described herein in the extruding fluid during operation of such osmotic device is desirable. For the particles to be well entrained, the agent drug form is dispersed in the fluid before the particles have an opportunity to settle in the tablet core. One means of accomplishing this is by adding a disintegrant that serves to break up the compressed core into its particulate components. Nonlimiting examples of standard disintegrants include materials such as sodium starch glycolate (e. g., Explotab™ CLV), microcrystalline cellulose (e. g., Avicel™), microcrystalline silicified cellulose (e. g., ProSolv™) and

croscarmellose sodium (e. g., Ac-Di-Sol™), and other disintegrants known to those skilled in the art. Depending upon the particular formulation, some disintegrants work better than others. Several disintegrants tend to form gels as they swell with water, thus hindering drug delivery from the device. Non-gelling, non-swelling disintegrants provide a more rapid dispersion of the drug particles within the core as water enters the core. In certain embodiments, non-gelling, non-swelling disintegrants are resins, for example, ion-exchange resins. In one embodiment, the resin is Amberlite™ IRP 88 (available from Rohm and Haas, Philadelphia, PA). When used, the disintegrant is present in amounts ranging from about 1-25% of the core agent.

[00195] Water-soluble polymers are added to keep particles of the agent suspended inside the device before they can be delivered through the passageway(s) (e.g., an orifice). High viscosity polymers are useful in preventing settling. However, the polymer in combination with the agent is extruded through the passageway(s) under relatively low pressures. At a given extrusion pressure, the extrusion rate typically slows with increased viscosity. Certain polymers in combination with particles of the agent described herein form high viscosity solutions with water but are still capable of being extruded from the tablets with a relatively low force. In contrast, polymers having a low weight-average, molecular weight (< about 300,000) do not form sufficiently viscous solutions inside the tablet core to allow complete delivery due to particle settling. Settling of the particles is a problem when such devices are prepared with no polymer added, which leads to poor drug delivery unless the tablet is constantly agitated to keep the particles from settling inside the core. Settling is also problematic when the particles are large and/or of high density such that the rate of settling increases.

[00196] In certain embodiments, the water-soluble polymers for such osmotic devices do not interact with the drug. In certain embodiments the water-soluble polymer is a non-ionic polymer. A nonlimiting example of a non-ionic polymer forming solutions having a high viscosity yet still extrudable at low pressures is Natrosol™ 250H (high molecular weight hydroxyethylcellulose, available from Hercules Incorporated, Aqualon Division, Wilmington, DE; MW equal to about 1 million daltons and a degree of polymerization equal to about 3,700). Natrosol

250H™ provides effective drug delivery at concentrations as low as about 3% by weight of the core when combined with an osmagent. Natrosol 250H™ NF is a high-viscosity grade nonionic cellulose ether that is soluble in hot or cold water. The viscosity of a 1% solution of Natrosol 250H using a Brookfield LVT (30 rpm) at 25°C is between about 1, 500 and about 2,500 cps.

[00197] In certain embodiments, hydroxyethylcellulose polymers for use in these monolayer osmotic tablets have a weight-average, molecular weight from about 300,000 to about 1.5 million. The hydroxyethylcellulose polymer is typically present in the core in an amount from about 2.0% to about 35% by weight.

[00198] Another example of an osmotic device is an osmotic capsule. The capsule shell or portion of the capsule shell can be semipermeable. The capsule can be filled either by a powder or liquid consisting of an agent described herein, excipients that imbibe water to provide osmotic potential, and/or a water-swellable polymer, or optionally solubilizing excipients. The capsule core can also be made such that it has a bilayer or multilayer agent analogous to the bilayer, trilayer or concentric geometries described above.

[00199] Another class of osmotic device useful in this invention comprises coated swellable tablets, for example, as described in EP378404. Coated swellable tablets comprise a tablet core comprising an agent described herein and a swelling material, preferably a hydrophilic polymer, coated with a membrane, which contains holes, or pores through which, in the aqueous use environment, the hydrophilic polymer can extrude and carry out the agent. Alternatively, the membrane may contain polymeric or low molecular weight water-soluble porosigens. Porosigens dissolve in the aqueous use environment, providing pores through which the hydrophilic polymer and agent may extrude. Examples of porosigens are water-soluble polymers such as HPMC, PEG, and low molecular weight compounds such as glycerol, sucrose, glucose, and sodium chloride. In addition, pores may be formed in the coating by drilling holes in the coating using a laser or other mechanical means. In this class of osmotic devices, the membrane material may comprise any film-forming polymer, including polymers which are water permeable or impermeable, providing that the membrane deposited on the tablet core is porous or contains water-soluble porosigens

or possesses a macroscopic hole for water ingress and drug release. Embodiments of this class of sustained release devices may also be multilayered, as described, for example, in EP378404.

[00200] When an agent described herein is a liquid or oil, such as a lipid vehicle formulation, for example as described in WO05/011634, the osmotic controlled-release device may comprise a soft-gel or gelatin capsule formed with a composite wall and comprising the liquid formulation where the wall comprises a barrier layer formed over the external surface of the capsule, an expandable layer formed over the barrier layer, and a semipermeable layer formed over the expandable layer. A delivery port connects the liquid formulation with the aqueous use environment. Such devices are described, for example, in US6419952, US6342249, US5324280, US4672850, US4627850, US4203440, and US3995631.

[00201] The osmotic controlled release devices of the present invention can also comprise a coating. In certain embodiments, the osmotic controlled release device coating exhibits one or more of the following features: is water-permeable, has at least one port for the delivery of drug, and is non-dissolving and non-eroding during release of the drug formulation, such that drug is substantially entirely delivered through the delivery port(s) or pores as opposed to delivery primarily via permeation through the coating material itself. Delivery ports include any passageway, opening or pore whether made mechanically, by laser drilling, by pore formation either during the coating process or *in situ* during use or by rupture during use. In certain embodiments, the coating is present in an amount ranging from about 5 to 30 wt% (including, for example, 10 to 20 wt%) relative to the core weight.

[00202] One form of coating is a semipermeable polymeric membrane that has the port(s) formed therein either prior to or during use. Thickness of such a polymeric membrane may vary between about 20 and 800 μm (including, for example, between about 100 to 500 μm). The diameter of the delivery port (s) may generally range in size from 0.1 to 3000 μm or greater (including, for example, from about 50 to 3000 μm in diameter). Such port(s) may be formed post-coating by mechanical or laser drilling or may be formed *in situ* by rupture of the coatings; such rupture may be controlled by intentionally incorporating a relatively small weak portion into the

coating. Delivery ports may also be formed *in situ* by erosion of a plug of water-soluble material or by rupture of a thinner portion of the coating over an indentation in the core. In addition, delivery ports may be formed during coating, as in the case of asymmetric membrane coatings of the type disclosed in US5612059 and US5698220. The delivery port may be formed *in situ* by rupture of the coating, for example, when a collection of beads that may be of essentially identical or of a variable agent are used. Drug is primarily released from such beads following rupture of the coating and, following rupture, such release may be gradual or relatively sudden. When the collection of beads has a variable agent, the agent may be chosen such that the beads rupture at various times following administration, resulting in the overall release of drug being sustained for a desired duration.

[00203] Coatings may be dense, microporous or asymmetric, having a dense region supported by a thick porous region such as those disclosed in US5612059 and US5698220. When the coating is dense the coating can be composed of a water-permeable material. When the coating is porous, it may be composed of either a water-permeable or a water-impermeable material. When the coating is composed of a porous water-impermeable material, water permeates through the pores of the coating as either a liquid or a vapor. Nonlimiting examples of osmotic devices that utilize dense coatings include US3995631 and US3845770. Such dense coatings are permeable to the external fluid such as water and may be composed of any of the materials mentioned in these patents as well as other water-permeable polymers known in the art.

[00204] The membranes may also be porous as disclosed, for example, in US5654005 and US5458887 or even be formed from water-resistant polymers. US5120548 describes another suitable process for forming coatings from a mixture of a water-insoluble polymer and a leachable water-soluble additive. The porous membranes may also be formed by the addition of pore-formers as disclosed in US4612008. In addition, vapor-permeable coatings may even be formed from extremely hydrophobic materials such as polyethylene or polyvinylidene difluorid that, when dense, are essentially water-impermeable, as long as such coatings are porous. Materials useful in forming the coating include but are not limited to various

grades of acrylic, vinyls, ethers, polyamides, polyesters and cellulosic derivatives that are water-permeable and water-insoluble at physiologically relevant pHs, or are susceptible to being rendered water-insoluble by chemical alteration such as by crosslinking. Nonlimiting examples of suitable polymers (or crosslinked versions) useful in forming the coating include plasticized, unplasticized and reinforced cellulose acetate (CA), cellulose diacetate, cellulose triacetate, CA propionate, cellulose nitrate, cellulose acetate butyrate (CAB), CA ethyl carbamate, CAP, CA methyl carbamate, CA succinate, cellulose acetate trimellitate (CAT), CA dimethylaminoacetate, CA ethyl carbonate, CA chloroacetate, CA ethyl oxalate, CA methyl sulfonate, CA butyl sulfonate, CA p-toluene sulfonate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, acetaldehyde dimethyl acetate, triacetate of locust bean gum, hydroxiated ethylene-vinylacetate, EC, PEG, PPG, PEG/PPG copolymers, PVP, HEC, HPC, CMC, CMEC, HPMC, HPMCP, HPMCAS, HPMCAT, poly (acrylic) acids and esters and poly- (methacrylic) acids and esters and copolymers thereof, starch, dextran, dextrin, chitosan, collagen, gelatin, polyalkenes, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes and synthetic waxes. In various embodiments, the coating agent comprises a cellulosic polymer, in particular cellulose ethers, cellulose esters and cellulose ester-ethers, i.e., cellulosic derivatives having a mixture of ester and ether substituents, the coating materials are made or derived from poly (acrylic) acids and esters, poly (methacrylic) acids and esters, and copolymers thereof, the coating agent comprises cellulose acetate, the coating comprises a cellulosic polymer and PEG, the coating comprises cellulose acetate and PEG.

[00205] Coating is conducted in conventional fashion, typically by dissolving or suspending the coating material in a solvent and then coating by dipping, spray coating or by pan-coating. In certain embodiments, the coating solution contains 5 to 15 wt% polymer. Typical solvents useful with the cellulosic polymers mentioned above include but are not limited to acetone, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, nitroethane, nitropropane, tetrachloroethane, 1,4-

dioxane, tetrahydrofuran, diglyme, water, and mixtures thereof. Pore-formers and non-solvents (such as water, glycerol and ethanol) or plasticizers (such as diethyl phthalate) may also be added in any amount as long as the polymer remains soluble at the spray temperature. Pore-formers and their use in fabricating coatings are described, for example, in US5612059. Coatings may also be hydrophobic microporous layers wherein the pores are substantially filled with a gas and are not wetted by the aqueous medium but are permeable to water vapor, as disclosed, for example, in US5798119. Such hydrophobic but water-vapor permeable coatings are typically composed of hydrophobic polymers such as polyalkenes, polyacrylic acid derivatives, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes and synthetic waxes. Hydrophobic microporous coating materials include but are not limited to polystyrene, polysulfones, polyethersulfones, polyethylene, polypropylene, polyvinyl chloride, polyvinylidene fluoride and polytetrafluoroethylene. Such hydrophobic coatings can be made by known phase inversion methods using any of vapor-quench, liquid quench, thermal processes, leaching soluble material from the coating or by sintering coating particles. In thermal processes, a solution of polymer in a latent solvent is brought to liquid-liquid phase separation in a cooling step. When evaporation of the solvent is not prevented, the resulting membrane will typically be porous. Such coating processes may be conducted by the processes disclosed, for example, in US4247498, US4490431 and US4744906. Osmotic controlled-release devices may be prepared using procedures known in the pharmaceutical arts. See for example, Remington: The Science and Practice of Pharmacy, 20th Edition, 2000.

[00206] As further noted above, the agents described herein may be provided in the form of microparticulates, generally ranging in size from about 10μm to about 2mm (including, for example, from about 100μm to 1mm in diameter). Such multiparticulates may be packaged, for example, in a capsule such as a gelatin capsule or a capsule formed from an aqueous-soluble polymer such as HPMCAS, HPMC or starch; dosed as a suspension or slurry in a liquid; or they may be formed into a tablet, caplet, or pill by compression or other processes known in the art. Such multiparticulates may be made by any known process, such as wet- and dry-

granulation processes, extrusion/spheronization, roller-compaction, melt-congealing, or by spray-coating seed cores. For example, in wet-and dry- granulation processes, the agent described herein and optional excipients may be granulated to form multiparticulates of the desired size. Other excipients, such as a binder (e. g., microcrystalline cellulose), may be blended with the agent to aid in processing and forming the multiparticulates. In the case of wet granulation, a binder such as microcrystalline cellulose may be included in the granulation fluid to aid in forming a suitable multiparticulate. See, for example, Remington : The Science and Practice of Pharmacy, 20"Edition, 2000. In any case, the resulting particles may themselves constitute the therapeutic composition or they may be coated by various film-forming materials such as enteric polymers or water-swellable or water-soluble polymers, or they may be combined with other excipients or vehicles to aid in dosing to patients.

[00207] In certain embodiments, it may be desirable to provide for the immediate release of one or more of the agents described herein, and the controlled release of one or more other agents. For example, in one embodiment, a compound described herein can be provided in an immediate release formulation together with a fibrate (e.g., Tricor) or a CETP inhibitor (e.g., torcetrapib) in a controlled release format. In another embodiment, a compound described herein can be provided together with an HMG CoA reductase inhibitor in an immediate release formulation. For example, a compound described herein can be coformulated with an HMG CoA reductase inhibitor in the immediate release formulation described in WO05/011634 (page 29, line 31 to page 33 (entire page). In other embodiments, a compound described herein is provided in a controlled release format together with another agent (e.g., an HMG CoA reductase inhibitor) in an immediate release formulation. In other embodiments, one or more agents described herein (for example, a compound described herein and an HMG CoA reductase inhibitor) can be provided in an immediate release formulation together with one or more other agents (for example, a fibrate and/or torcetrapib) in a controlled release format.

[00208] The agents can be administered, e.g., by intravenous injection, intramuscular injection, subcutaneous injection, intraperitoneal injection, topical, sublingual, intraarticular (in the joints), intradermal, buccal, ophthalmic (including

intraocular), intranasaly (including using a cannula), or by other routes. The agents can be administered orally, e.g., as a tablet or cachet containing a predetermined amount of the active ingredient, gel, pellet, paste, syrup, bolus, electuary, slurry, capsule, powder, granules, as a solution or a suspension in an aqueous liquid or a non-aqueous liquid, as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion, via a micellar formulation (see, e.g., WO 97/11682) via a liposomal formulation (see, e.g., EP 736299,WO 99/59550 and WO 97/13500), via formulations described in WO 03/094886 or in some other form. Orally administered compositions can include binders, lubricants, inert diluents, lubricating, surface active or dispersing agents, flavoring agents, and humectants. Orally administered formulations such as tablets may optionally be coated or scored and may be formulated so as to provide sustained, delayed or controlled release of the active ingredient therein. The agents can also be administered transdermally (i.e. via reservoir-type or matrix-type patches, microneedles, thermal poration, hypodermic needles, iontophoresis, electroporation, ultrasound or other forms of sonophoresis, jet injection, or a combination of any of the preceding methods (Prausnitz et al. 2004, Nature Reviews Drug Discovery 3:115)). The agents can be administered locally, for example, at the site of injury to an injured blood vessel. The agents can be coated on a stent. The agents can be administered using high-velocity transdermal particle injection techniques using the hydrogel particle formulation described in U.S. 20020061336. Additional particle formulations are described in WO 00/45792, WO 00/53160, and WO 02/19989. An example of a transdermal formulation containing plaster and the absorption promoter dimethylisosorbide can be found in WO 89/04179. WO 96/11705 provides formulations suitable for transdermal administration. The agents can be administered in the form a suppository or by other vaginal or rectal means. The agents can be administered in a transmembrane formulation as described in WO 90/07923. The agents can be administered non-invasively via the dehydrated particles described in U.S. 6,485,706. The agent can be administered in an enteric-coated drug formulation as described in WO 02/49621. The agents can be administered intranasaly using the formulation described in U.S. 5,179,079. Formulations suitable for parenteral injection are described in WO 00/62759. The agents can be administered using the

casein formulation described in U. S. 20030206939 and WO 00/06108. The agents can be administered using the particulate formulations described in U.S. 20020034536.

[00209] The agents, alone or in combination with other suitable components, can be administered by pulmonary route utilizing several techniques including but not limited to intratracheal instillation (delivery of solution into the lungs by syringe), intratracheal delivery of liposomes, insufflation (administration of powder formulation by syringe or any other similar device into the lungs) and aerosol inhalation. Aerosols (e.g., jet or ultrasonic nebulizers, metered-dose inhalers (MDIs), and dry-powder inhalers (DPIs)) can also be used in intranasal applications. Aerosol formulations are stable dispersions or suspensions of solid material and liquid droplets in a gaseous medium and can be placed into pressurized acceptable propellants, such as hydrofluroalkanes (HFAs, i.e. HFA-134a and HFA-227, or a mixture thereof), dichlorodifluoromethane (or other chlorofluocarbon propellants such as a mixture of Propellants 11, 12, and/or 114), propane, nitrogen, and the like. Pulmonary formulations may include permeation enhancers such as fatty acids, and saccharides, chelating agents, enzyme inhibitors (e.g., protease inhibitors), adjuvants (e.g., glycocholate, surfactin, span 85, and nafamostat), preservatives (e.g., benzalkonium chloride or chlorobutanol), and ethanol (normally up to 5% but possibly up to 20%, by weight). Ethanol is commonly included in aerosol compositions as it can improve the function of the metering valve and in some cases also improve the stability of the dispersion. Pulmonary formulations may also include surfactants which include but are not limited to bile salts and those described in U.S. 6,524,557 and references therein. The surfactants described in U.S. 6,524,557, e.g., a C8-C16 fatty acid salt, a bile salt, a phospholipid, or alkyl saccharide are advantageous in that some of them also reportedly enhance absorption of the compound in the formulation. Also suitable in the invention are dry powder formulations comprising a therapeutically effective amount of active compound blended with an appropriate carrier and adapted for use in connection with a dry-powder inhaler. Absorption enhancers which can be added to dry powder formulations of the present invention include those described in U.S. 6,632,456. WO 02/080884 describes new methods for the surface modification of

powders. Aerosol formulations may include U.S. 5,230,884, U.S. 5,292,499, WO 017/8694, WO 01/78696, U.S. 2003019437, U. S. 20030165436, and WO 96/40089 (which includes vegetable oil). Sustained release formulations suitable for inhalation are described in U.S. 20010036481A1, 20030232019A1, and U.S. 20040018243A1 as well as in WO 01/13891, WO 02/067902, WO 03/072080, and WO 03/079885. Pulmonary formulations containing microparticles are described in WO 03/015750, U.S. 20030008013, and WO 00/00176. Pulmonary formulations containing stable glassy state powder are described in U.S. 20020141945 and U.S. 6,309,671. Other aerosol formulations are described in EP 1338272A1 WO 90/09781, U. S. 5,348,730, U.S. 6,436,367, WO 91/04011, and U.S. 6,294,153 and U.S. 6,290,987 describes a liposomal based formulation that can be administered via aerosol or other means. Powder formulations for inhalation are described in U.S. 20030053960 and WO 01/60341. The agents can be administered intranasally as described in U.S. 20010038824.

[00210] Solutions of medicament in buffered saline and similar vehicles are commonly employed to generate an aerosol in a nebulizer. Simple nebulizers operate on Bernoulli's principle and employ a stream of air or oxygen to generate the spray particles. More complex nebulizers employ ultrasound to create the spray particles. Both types are well known in the art and are described in standard textbooks of pharmacy such as Sprowls' American Pharmacy and Remington's The Science and Practice of Pharmacy. Other devices for generating aerosols employ compressed gases, usually hydrofluorocarbons and chlorofluorocarbons, which are mixed with the medicament and any necessary excipients in a pressurized container, these devices are likewise described in standard textbooks such as Sprowls and Remington.

[00211] The agent can be incorporated into a liposome to improve half-life. The agent can also be conjugated to polyethylene glycol (PEG) chains. Methods for pegylation and additional formulations containing PEG-conjugates (i.e. PEG-based hydrogels, PEG modified liposomes) can be found in Harris and Chess, Nature Reviews Drug Discovery 2: 214-221 and the references therein. The agent can be administered via a nanocochleate or cochleate delivery vehicle (BioDelivery Sciences International). The agents can be delivered transmucosally (i.e. across a mucosal

surface such as the vagina, eye or nose) using formulations such as that described in U.S. 5,204,108. The agents can be formulated in microcapsules as described in WO 88/01165. The agent can be administered intra-orally using the formulations described in U.S. 20020055496, WO 00/47203, and U.S. 6,495,120. The agent can be delivered using nanoemulsion formulations described in WO 01/91728A2.

Administration and formulation of combitherapy protein/peptide agents

[00212] Some of the agents used in combitherapy with compounds described herein are proteins (e.g., nitric oxide synthase isoforms, HDL associated proteins such as ApoA-I or Apo A-I Milano) or peptides (e.g., peptides which mitigates one or more symptoms of atherosclerosis, peptides and peptide analogues that mimic the structural and pharmacological properties of human ApoA-I, Exenatide®). In some embodiments, the recombinant or purified protein is administered together with a compound described herein. In alternative embodiments, genes encoding the protein or peptide to be delivered may be administered, rather than the protein. Gene transfer can be obtained using direct transfer of genetic material, in a plasmid or viral vector, or via transfer of genetic material in cells or carriers such as cationic liposomes. Such methods are well known in the art and readily adaptable for use in the therapies described herein. For example, studies by Wolff et al., Biotechniques 11:474-85 (1991), demonstrate injection of naked DNA into muscle allows long term and low expression levels of proteins coded for within the DNA sequence. Administration of naked DNA to smooth muscle layers can be achieved by use of an intramural device, such as an INFILTRATOR™ and allow expression of the proteins or their alpha helical domains to treat the injured vessel. Transfer vectors can be any nucleotide construction used to deliver genes into cells (e.g., a plasmid), or as part of a general strategy to deliver genes, e.g., as part of recombinant retrovirus or adenovirus (Ram et al. Cancer Res. 53:83-88, (1993)). Appropriate means for transfection, including viral vectors, chemical transfectants, or physico-mechanical methods such as electroporation and direct diffusion of DNA, are described by, for example, Wolff, J. A., et al., Science, 247, 1465-1468, (1990); and Wolff, J. A. Nature, 352, 815-818, (1991). Plasmid or viral vectors are agents that transport the gene into a cell without

degradation and may include a promoter yielding expression of the gene in the cell into which it is delivered. In certain embodiments vectors are derived from either a virus or a retrovirus. Viral vectors include but are not limited to those derived from Adenovirus, Adeno-associated virus, Herpes virus, Vaccinia virus, Polio virus, AIDS virus, neuronal trophic virus, Sindbis and other RNA viruses, including these viruses with the HIV backbone. Vectors from other viral families which share the properties of these viruses may make them suitable for use as vectors. Retroviral vectors include but are not limited to those derived from include Murine Maloney Leukemia virus, MMLV, and retroviruses that express the desirable properties of MMLV as a vector. In certain emobodiments where non-proliferating cells are involved, retroviral vectors are not used. Retroviral vectors, in general, are described by Verma, I. M., Retroviral vectors for gene transfer. In MICROBIOLOGY-1985, American Society for Microbiology, pp. 229-232, Washington, (1985). Examples of methods for using retroviral vectors for gene therapy are described in US4868116, US4980286, WO90/02806, WO 89/07136 and Mulligan, (Science 260:926-932 (1993)).

[00213] Adenovirus vectors are relatively stable and easy to work with, have high titers, and can be delivered in aerosol formulation, and can transfect non-dividing cells. The construction of replication-defective adenoviruses has been described (Berkner et al., J. Virology 61:1213-1220 (1987); Massie et al., Mol. Cell. Biol. 6:2872-2883 (1986); Haj-Ahmad et al., J. Virology 57:267-274 (1986); Davidson et al., J. Virology 61:1226-1239 (1987); Zhang "Generation and identification of recombinant adenovirus by liposome-mediated transfection and PCR analysis" BioTechniques 15:868-872 (1993)). Adenoviral derived vectors are limited in the extent to which they can spread to other cell types, since they can replicate within an initial infected cell, but are unable to form new infectious viral particles. Recombinant adenoviruses have been shown to achieve high efficiency gene transfer after direct, in vivo delivery to airway epithelium, hepatocytes, vascular endothelium, CNS parenchyma and a number of other tissue sites (Morsy, J. Clin. Invest. 92:1580-1586 (1993); Kirshenbaum, J. Clin. Invest. 92:381-387 (1993); Roessler, J. Clin. Invest. 92:1085-1092 (1993); Moullier, Nature Genetics 4:154-159 (1993); La Salle, Science 259:988-990 (1993); Gomez-Foix, J. Biol. Chem. 267:25129-25134 (1992); Rich,

Human Gene Therapy 4:461-476 (1993); Zabner, Nature Genetics 6:75-83 (1994); Guzman, Circulation Research 73:1201-1207 (1993); Bout, Human Gene Therapy 5:3-10 (1994); Zabner, Cell 75:207-216 (1993); Caillaud, Eur. J. Neuroscience 5:1287-1291 (1993); and Ragot, J. Gen. Virology 74:501-507 (1993)). Pox viral vectors can be used in the gene transfer techniques described herein. In certain embodiment the viral/retroviral vector used in the gene transfer techniques described herein have been engineered so as to suppress the immune response of the host organism, elicited by the viral antigens. In certain embodiments, these vectors carry coding regions for Interleukin 8 or 10. In certain embodiments, the viral/retroviral vectors described herein have one or more of the early genes removed and a gene or gene/promotor cassette inserted into the viral genome in place of the removed viral DNA.

[00214] The inserted genes in viral/retroviral vectors usually contain promoters, and/or enhancers to help control the expression of the desired gene product. A promoter is generally a sequence or sequences of DNA that function when in a relatively fixed location in regard to the transcription start site. A promoter contains core elements required for basic interaction of RNA polymerase and transcription factors, and may contain upstream elements and response elements. Promoters controlling transcription from vectors in mammalian host cells may be obtained from various sources, for example, the genomes of viruses such as: polyoma, Simian Virus 40 (SV40), adenovirus, retroviruses, hepatitis-B virus and most preferably cytomegalovirus, or from heterologous mammalian promoters, e.g., beta actin promoter. The early and late promoters of the SV40 virus are conveniently obtained as an SV40 restriction fragment which also contains the SV40 viral origin of replication (Fiers et al., Nature, 273:113 (1978)). The immediate early promoter of the human cytomegalovirus is conveniently obtained as a HindIII E restriction fragment (Greenway, P. J. et al., Gene 18:355-360 (1982)). Promoters from the host cell (to which the viral vector is being transferred) or related species also are useful herein.

[00215] Enhancer generally refers to a sequence of DNA that functions at no fixed distance from the transcription start site and can be either 5' (Laimins, L. et al., Proc. Natl. Acad. Sci. 78:993 (1981)) or 3' (Lusky, M. L., et al., Mol. Cell Bio. 3:1108

(1983)) to the transcription unit. Furthermore, enhancers can be within an intron (Banerji, J. L. et al., Cell 33:729 (1983)) as well as within the coding sequence itself (Osborne, T. F., et al., Mol. Cell Bio. 4:1293 (1984)). They are usually between 10 and 300 bp in length, and they function in cis. Enhancers function to increase transcription from nearby promoters. Enhancers also often contain response elements that mediate the regulation of transcription. Promoters can also contain response elements that mediate the regulation of transcription. Enhancers often determine the regulation of expression of a gene. While many enhancer sequences are now known from mammalian genes (globin, elastase, albumin, α-fetoprotein and insulin), typically one will use an enhancer from a eukaryotic cell virus. Enhancers include but are not limited to the SV 40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers.

[00216] The promotor and/or enhancer may be specifically activated either by light or specific chemical events which trigger their function. Systems can be regulated by reagents such as tetracycline and dexamethasone. There are also ways to enhance viral vector gene expression by exposure to irradiation, such as gamma irradiation, or alkylating chemotherapy drugs.

[00217] In certain embodiments, the promoter and/or enhancer region act as a constitutive promoter and/or enhancer to maximize expression of the region of the transcription unit to be transcribed. In certain embodiments the promoter and/or enhancer region is active in all eukaryotic cell types. Promoters include but are not limited to the CMV promoter (650 bases), SV40 promoters, cytomegalovirus (full length promoter), and retroviral vector LTF.

[00218] Expression vectors used in eukaryotic host cells may also contain sequences necessary for the termination of transcription which may affect mRNA expression. These regions are transcribed as polyadenylated segments in the untranslated portion of the mRNA encoding tissue factor protein. The 3' untranslated regions also include transcription termination sites. In certain embodiments, the transcription unit also contains a polyadenylation region (e.g., that derived from the SV40 early polyadenylation signal consisting of about 400 bases). One benefit of this region is

that it increases the likelihood that the transcribed unit will be processed and transported like mRNA. The identification and use of polyadenylation signals in expression constructs is well established. In certain embodiments, homologous polyadenylation signals are used in the transgene constructs. In certain embodiments, the transcribed units contain other standard sequences alone or in combination with the above sequences improve expression from, or stability of, the construct.

[00219] The viral/retroviral vectors can include nucleic acid sequence encoding a marker product. This marker product is used to determine if the gene has been delivered to the cell and once delivered is being expressed. Examples of suitable selectable markers for mammalian cells are dihydrofolate reductase (DHFR), thymidine kinase, neomycin, neomycin analog G418, hydromycin, and puromycin. When such selectable markers are successfully transferred into a mammalian host cell, the transformed mammalian host cell can survive if placed under selective pressure.

Kits

[00220] The compounds and pharmaceutical formulations described herein may be contained in a kit. The kit may include single or multiple doses of two or more agents, each packaged or formulated individually, or single or multiple doses of two or more agents packaged or formulated in combination. Thus, one or more agents can be present in first container, and the kit can optionally include one or more agents in a second container. The container or containers are placed within a package, and the package can optionally include administration or dosage instructions. A kit can include additional components such as syringes or other means for administering the agents as well as diluents or other means for formulation. Thus, the kits can comprise: a) a pharmaceutical composition comprising a compound described herein and a pharmaceutically acceptable carrier, vehicle or diluent; and b) a container or packaging. The kits may optionally comprise instructions describing a method of using the pharmaceutical compositions in one or more of the methods described herein (e.g., preventing or treating vascular diseases/disorders and conditions (including but not limited to arteriosclerosis, atherosclerosis, cardiovascular disease, cerebrovascular disease, renovascular disease, mesenteric vascular disease, pulmonary vascular disease, ocular vascular disease and peripheral vascular disease),

hyperlipidemia (including but not limited to hypercholesterolemia, hypertriglyceridemia, sitosterolemia), hypertension, angina, cardiac arrhythmias, congestive heart failure, and stroke). The kit may optionally comprise a second pharmaceutical composition comprising one or more additional agents chosen from (1) a dyslipidemic agent, (2) an anti-diabetic agent, (3) an anti-hypertensive agent, (4) an anti-obesity agent, (5) an agent used to treat autoimmune disorders, (6) an agent used to treat demylenation and its associated disorders, (7) an agent used to treat Alzheimer's disease, (8) a blood modifier, (9) a hormone replacement agent/composition, (10) a chemotherapeutic agent, (11) a peptide which mitigates one or more symptoms of atherosclerosis, (12) an anti-cancer agent, and (13) an agent used to treat bone loss and associated disorders and a pharmaceutically acceptable carrier, vehicle or diluent. The pharmaceutical composition comprising the compound described herein and the second pharmaceutical composition contained in the kit may be optionally combined in the same pharmaceutical composition.

[00221] A kit includes a container or packaging for containing the pharmaceutical compositions and may also include divided containers such as a divided bottle or a divided foil packet. The container can be, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle which is in turn contained within a box.

[00222] An example of a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process, recesses are formed in the plastic foil. The recesses have the size and shape of individual tablets or capsules to be packed or may have the size and shape to accommodate multiple tablets and/or capsules to be packed. Next, the tablets or capsules are placed in the recesses

accordingly and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are individually sealed or collectively sealed, as desired, in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

[00223] It maybe desirable to provide a written memory aid containing information and/or instructions for the physician, pharmacist or subject regarding when the medication is to be taken. A "daily dose" can be a single tablet or capsule or several tablets or capsules to be taken on a given day. When the kit contains separate compositions, a daily dose of one or more compositions of the kit can consist of one tablet or capsule while a daily dose of another one or more compositions of the kit can consist of several tablets or capsules. A kit can take the form of a dispenser designed to dispense the daily doses one at a time in the order of their intended use. The dispenser can be equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter which indicates the number of daily doses that have been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

In Vivo Animal Models

[00224] In Vivo Assay of Hypolipidemic Agents using the Rat Cholesterol Absorption Model. This model is based on models described by Burnett et al (2002), Bioorg. Med. Chem. Lett. 2002 Feb 11;12(3):315-8 and J. Lipid Res. 1999 Oct;40(10):1747-57. Female Sprague-Dawley rats weighing 150-250g were separated into groups of 3 and fasted overnight. The animals (4-6/group) were dosed perorally with 300μL test compounds in olive oil or suitable vehicle. Thirty minutes later, 3-5 microCuries ^{3}H-cholesterol per rat were delivered perorally in 300 μL olive oil . After

three hours, 200 μL serum was collected, vortexed with scintillation fluid, and measured for radioactivity in a scintillation counter. Percent inhibition is defined as $100*(1-C_{test}/C_{ctrl})$, where C_{test} and C_{ctrl} refer to ^3H levels in serum for the test compound and for the vehicle only control, respectively. Percent inhibition values are reported for a fixed dose. The ED_{50} is the dose at which the half-maximal effect on serum ^3H levels is observed for a given test compound.

[00225] In Vivo Assay of Hypolipidemic Agents using the Mouse Cholesterol Absorption Model. Female CD-1 mice weighing 20-30g were separated into groups of 3-8 and fasted overnight. The animals (3-8/group) were dosed perorally with 200μL test compound in olive oil or suitable vehicle. Thirty minutes later, 3-5 microCuries ^3H-cholesterol per mouse were delivered perorally in 200 μL olive oil. After three hours, 100 μL serum was collected, vortexed with scintillation fluid, and measured for radioactivity in a scintillation counter. Percent inhibition and ED_{50} are defined as in the Rat Cholesterol Absorption Model above.

[00226] In Vivo Assay of Hypolipidemic Agents Using the Hyperlipidemic Hamster: Hamsters were separated into groups of six and given a controlled cholesterol diet (Purina Chow #5001 containing 0.5% cholesterol) for seven days. Diet consumption was monitored to determine dietary cholesterol exposure in the face of test compounds. The animals were dosed with the test compound once daily beginning with the initiation of diet. Dosing was by oral gavage of 0.2 mL of corn oil alone (control group) or solution (or suspension) of test compound in corn oil. All animals moribund or in poor physical condition were euthanized. After seven days, the animals were anesthetized by intramuscular (IM) injection of ketamine and sacrificed by decapitation. Blood was collected into vacutainer tubes containing EDTA for plasma lipid analysis and the liver excised for tissue lipid analysis. Lipid analysis was conducted as per published procedures [Schnitzer-Polokoff, R., et al, Comp. Biochem. Physiol., 99A, 4, 665-670 (1991)] and data are reported as percent reduction of lipid versus control.

[00227] In Vivo Assay of Hypolipidemic Agents using the Hamster Acute Cholesterol Absorption Model. Male Syrian Hamsters weighing approximately 120g were separated into groups of 3-6 and fasted overnight. The animals (3-6/group) were

dosed perorally with 200μL test compound in olive oil or suitable vehicle. Thirty minutes later, 3-5 microCuries ^{3}H-cholesterol per hamster were delivered perorally in 200 μL olive oil. After three hours, 100-200 μL serum was collected, vortexed with scintillation fluid, and measured for radioactivity in a scintillation counter. Percent inhibition and ED_{50} are defined as in the Rat Cholesterol Absorption Model above.

[00228] The bioabsorption of the compounds herein described may be examined using the Caco-2 cell monolayer model of Hilgers et al. [Pharm. Res. 7, 902 (1990)].

Pharmacokinetics

[00229] To study the pharmacokinetics of compounds, bioavailability studies were carried out in various test animals. Compounds were prepared in suitable formulations for oral and intravenous administration. Compounds were administered via intravenous injection (tail vein (rat), femoral vain (hamster), peripheral vain (monkey), cephalic vein (dog)) and orally (via a capsule (dogs) or gavage (all others)) to independent groups of test animals which were either fasted overnight or non-fasted. Serum or plasma was collected at various time points and assayed for the presence of compounds using an LC/MS/MS detection method. Experiment samples were either diluted 15-fold in 30% acetonitrile in water, injected onto an in-line sample extraction cartridge (Waters Oasis HLB Direct Connect) and loaded onto a reverse phase HPLC column fitted with a appropriate guard column or prepared using a protein crash, dried under nitrogen, resuspended in 30% acetonitrile in water and loaded onto a reverse phase HPLC column fitted with a appropriate guard column. Samples were eluted from the reverse phase HPLC column with a gradient. A Micromass Quattro Micro (Waters Corporation, Milford, MA) triple quadrupole mass spectrometer operated in MRM mode was used for detection. Concentrations were calculated based on a standard concentration curve of compound or standard curves generated using peak area ratio of compound to internal standard vs. concentration. MassLynx software (Waters, Corporation, Milford, MA) was used to calculate the absolute concentration of test compound in each serum or plasma sample. A concentration versus time plot was generated from the data in Microsoft Excel, Summit Software PK Solutions 2.0, GraphPad Prism (GraphPad Software, Inc., San Diego, CA) or WinNonlin Professional Version 4.1 (Pharsight Corporation, Mountain

View, CA) to generate pharmacokinetic curves. An area under the curve (AUC_n, n = length of experiment in minutes or hours) was calculated from the concentration vs. time data by software using the linear trapezoid method for both the orally and intravenously dosed animals. Oral Bioavailability (F) over the length of the experiment is calculated using the equation:

$$F = (AUC_{oral} * Dose_{i.v.}) / (AUC_{i.v.} * Dose_{oral}).$$

The bioavailability of several compounds of the invention tested one or more times in various animals is shown in Figure 1.

Determination of Acyl Coenzyme A: Cholesterol Acyltransferase (ACAT) Inhibition Activity

[00230] The ability of representative compounds of the invention to inhibit acyl-coenzyme A: cholesterol acyltransferase (ACAT) activity was assayed by measuring cholesterol esterification in human HepG2 and Caco2 cells. ACAT activity was measured by following the conversion of ^{14}C-oleic acid to ^{14}C-cholesteryl oleate in an assay based on Junquero, et al. 2001 Biochem Pharmacol 61:97-108 and Sugiyama, et al. Atherosclerosis 118:145-53. Cells were propagated in Eagle's Minimum Essential Medium (EMEM) supplemented with fetal bovine serum (10% for HepG2 cells; 20% for Caco2 cells) and 2 mM L-glutamine. All incubations were performed at 37 °C in air with 5% CO_2. In preparation for each experiment, cells were seeded in 6-well plates and allowed to grow to 90-95% confluency. All treatments were performed in duplicate. Inhibitors were pre-incubated with cells for 4 h. The assay was initiated by adding ^{14}C-oleate/bovine serum albumin solution to each assay well and incubating an additional 2 h at 37 °C. Cell monolayers were extracted with 2 mL 3:2 hexane:isopropanol at room temperature for 30 min. Extracts were dried down under nitrogen and dissolved in 75 ⌠L chloroform. Formation of ^{14}C-cholesteryl oleate was determined by separation of the ACAT assay reaction products by thin-layer chromatography (TLC) and visualization by phosphorimaging. Percent inhibition was calculated for each compound dose, and IC_{50} values were determined using GraphPad Prism by regression analysis of percent inhibition plotted as a function of the

logarithmic value of the sample concentration. Figure 2 is a table of the ACAT activity of several compounds of the invention assayed one or more times. The known ACAT inhibitor, N-[4-(2-chlorophenyl)-6,7-dimethyl-3-quinolyl]-N'-(2, 4-difluorophenyl) urea (TMP-153) was also determined. For comparison, Figure 2 also shows the IC_{50} value for the known cholesterol absorption inhibitor molecule, (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one, in this assay.

Competitive binding assays

[00231] The ability of several compounds of the invention to bind and compete for specific binding to a receptor in the hamster small intestine was tested. Competition binding to hamster small intestine was determined by using an in vivo assay based on Hernandez et al. 2000 (Biochim Biophys Acta 1486:232-242) in which radiolabeled compound is administered to hamsters in the presence and absence of unlabeled, test, competitor compounds. In this experiment, a compound of the invention, ^{3}H-(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol was used as the radioligand. Unlabeled (1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol in 1200-fold excess was used to demonstrate that the observed binding was specific. Several compounds of the invention and a known cholesterol absorption inhibitor, (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one, were evaluated for their ability to compete for binding of ^{3}H-(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol when administered in 1200-fold excess. Golden Syrian hamsters were fasted overnight prior to dosing. Animals were dosed by oral gavage with 0.5 ml of either vehicle or vehicle containing 0.35 mg/kg test compound. One hour later, animals were dosed by oral gavage with 5 ∫Ci ^{3}H-(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol

with vehicle or vehicle containing 0.35 mg/kg test compound as above. Three hours after administration of the ^{3}H-(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol, animals were euthanized by CO_2 overdose, the small intestine dissected, flushed with cold saline, and placed into an empty tube on ice. The small intestine was cut into ~6 cm segments. The intestinal epithelial mucosa was extruded from each segment, homogenized in PBS, and the radioactivity in the homogenate was counted by liquid scintillation counting. Results were normalized for protein content of the homogenates. ^{3}H-(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol binding to the hamster small intestine in the presence and absence of test compound was determined by calculating the average bound radioactivity per mg of protein (DPM/mg) for each treatment group. Percent ^{3}H-(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol binding was calculated for each compound using the formulas:

Bound Radioactivity (DPM/mg) = Radioactivity (DPM)/Total Protein (mg)

Percent ^{3}H Binding vs Vehicle Control =

$$100\% * ((\text{Bound Radioactivity})_{\text{competitor}}/(\text{Bound Radioactivity})_{\text{vehicle}})$$

Statistical analysis was performed using an unpaired, two-tailed, Student's t-test (GraphPad Prism). ^{3}*H*-(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol binding to the small intestine of hamsters in the presence or absence of competitor compounds is shown in Figure 3A and Figure 3B and the calculated percentage binding relative to control is displayed in Figure 3C.

[00232] A particularly desirable medicament would inhibit cholesterol absorption without affecting the acute absorption of other important molecules of dietary origin. Such a cholesterol absorption inhibitor would not interfere with the absorption of triglyceride, progesterone, ethinyl estradiol, vitamin A, vitamin D, or taurocholic acid. For example, cholestyramine, which is in clinical use to lower serum cholesterol, sequesters bile acids in the intestine, ultimately leading to a decrease in plasma

cholesterol by upregulating the synthesis of bile acids from cholesterol in the liver. Two side effects of cholestyramine are gastrointestinal discomfort and the sequestration of fat-soluble vitamins. On the other hand, ezetimibe, a known cholesterol absorption inhibitor, does not appear to affect fat-soluble vitamin absorption in humans. In addition, ezetimibe does not inhibit the absorption of taurocholic acid, suggesting that certain cholesterol absorption inhibitors can lower serum cholesterol without inhibiting the ileal Na+/bile acid cotransporter.

Retinol, taurocholic acid, progesterone, sitostanol, and cholesterol absorption assays

[00233] The effects of acute oral administration of several compounds of the invention on retinol, taurocholic acid, and progesterone absorption were studied in female Sprague Dawley rats. Groups of 5 rats received 10 mg/kg of test compound or vehicle (olive oil) via oral gavage. Test compounds were administered 30 minutes prior to oral administration of ^{14}C-cholesterol (5 μCi) in addition to either ^{3}H-retinol (3 μCi), ^{3}H-taurocholic acid (3 μCi), ^{3}H-progesterone (3 μCi), or ^{3}H-sitostanol (3 μCi) constituted in olive oil (300 μL). Blood was sampled from all animals via the retro-orbital sinus under isoflurane anesthesia three hours after the administration of the radiolabeled cocktail and again at 24 hours. Serum radioactivity (DPM) was measured and the percent absorption (% absorption) was calculated as:

average dpm treated group/average dpm control group x 100.

[00234] Figures 4A, B, C, and D are tables showing the effects of several compounds of the invention on retinol (24 hr timepoint), taurocholic acid (24 hr timepoint), and progesterone (3 hr timepoint), sitostanol (24 hr timepoint) and cholesterol absorption. For each of figures 4A, 4B, 4C and 4D, results using the known cholesterol absorption inhibitor molecule, (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one is provided for comparison.

Behavioral Assay

[00235] The compounds of the invention can be tested to determine their effects on general activity (e.g. behavioural, autonomic and motor capabilities), for example, using Irwin's method (Psychopharmacologia - 1968 13:222-57). Briefly, groups of rodents receive a single administration of vehicle or different doses of test compound by oral gavage. Irwin observations are performed at 30, 60, 90, 180 and 300 minutes post dosing. Animals are generally observed 7 days post dosing.

Electrophysiological Assays

[00236] hERG channels are expressed in a human embryonic kidney (HEK293) cell line that lacks endogenous I_{Kr}. HEK293 cells are stably transfected with hERG cDNA. Stable transfectants are selected by coexpression with the G418-resistance gene incorporated into the expression plasmid. Selection pressure is maintained by including G418 in the culture medium. Cells are cultured in Dulbecco's Modified Eagle Medium / Nutrient Mixture F-12 (D-MEM/F-12) supplemented with 10% fetal bovine serum, 100 U/mL penicillin G sodium, 100 μg/mL streptomycin sulfate and 500 μg/mL G418. Cells are maintained in tissue culture incubators at 37°C in a humidified 95% air, 5% CO_2 atmosphere, with stocks maintained in cryogenic storage. Cells used for electrophysiology are plated in plastic culture dishes.

[00237] Test solution, reference substance (E-4031, 500 nm) and positive control (terfenadine, 60 nm) are prepared fresh daily in HEPES-buffered physiological saline (HB-PS) solution (composition in mM): NaCl, 137; KCl, 4.0; $CaCl_2$, 1.8; $MgCl_2$, 1; HEPES, 10; Glucose, 10; pH adjusted to 7.4 with NaOH. All test and control solutions also contain 0.3% dimethylsulfoxide (DMSO). Thus the vehicle control solution is HB-PS + DMSO $\geq$ 0.3%.

[00238] Cells are transferred to the recording chamber and superfused with vehicle control solution. Micropipette solution for whole cell patch clamp recordings is composed of (mM): potassium aspartate, 130; $MgCl_2$, 5; EGTA, 5; ATP, 4; HEPES, 10; pH adjusted to 7.2 with KOH. The recording is performed at a temperature of 35 ± 2 °C. Micropipettes for patch clamp recording are made from glass capillary tubing

using a P-97 micropipette puller (Sutter Instruments, Novato, CA). A commercial patch clamp amplifier is used for whole cell recordings. Before digitization, current records are low-pass filtered at one-fifth of the sampling frequency.

[00239] Cells stably expressing hERG are held at -80 mV. Onset and steady state activation of hERG current due to test compound is measured using a pulse pattern with fixed amplitudes (conditioning prepulse: +20 mV for 1 sec; repolarizing test ramp to –80 mV (-0.5 V/s)) repeated at 5 s intervals. Each recording ends with a final application of a supramaximal concentration of the reference substance (E-4031, 500 nM), to assess the contribution of endogenous currents. The remaining unblocked current is subtracted off-line digitally from the data to determine the potency of the test substance for hERG activation.

[00240] Steady state is defined by the limiting constant rate of change with time (linear time dependence). The steady state before and after test article application is used to calculate the percentage of current inhibited at each concentration. Percent activation at each concentration in the test group is compared with the vehicle control group using one-way ANOVA followed by Dunnett's multiple comparison test (JMP Version 5.0.1, SAS Institute, Cary, NC).

[00241] Test compound at different concentrations is applied to cells to deterimine effect on hERG current amplitude. The average value of 3 cells for each group ± standard error of the mean (SEM) is determined and compared to the positive control terfenadine, a known hERG channel inhibitor.

[00242] Increases in QT duration and action potential duration in isolated guinea pig hearts can be used to indicate an arrhythmogenic effect. Hearts are perfused with an oxygenated Tyrode's solution, containing 0.0; 1.0; 5.0 or 10.0 μM of test compound. QT duration and action potential duration (APD) are measured from cardiac electrodes. In separate experiments, the hearts are divided into 2 subgroups receiving either the test compound or control to determine the respective effects on QT duration and APD.

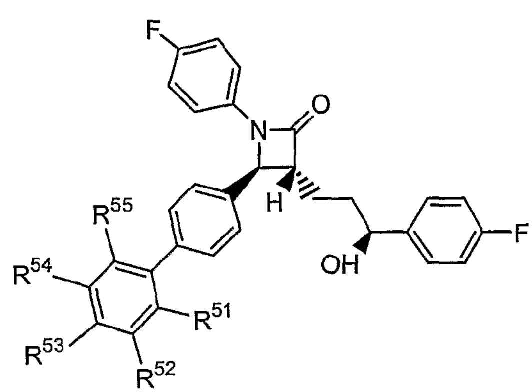
[00243] To observe the effects *in vivo*, mongrel dogs of either sex weighing 5-20 kg are anesthetized and instrumented by standard techniques for blood pressure and EKG. A solid state transducer for dP/dT is placed in the left cardiac ventricle, and an

epicardial electrode is put into place. The test compound is infused followed by terfenadine at progressively higher doses, beginning at 1 µg/kg/min for 15 minutes and increased incrementally until a cardiovascular collapse ensues. Parameters measured are: blood pressure, heart rate, dP/dT, and the QT-interval. From the QT interval and the heart rate, a QTc interval may be calculated. Measurements of hemodynamics and electrical activity are made in response to the test compound and to control.

[00244] Electrophysiological effects of test compounds as a function of extracellular potassium and cycle length can be assessed using standard microelectrode techniques in canine Purkinje fibers (Gintant *et al.* 2001 J.Cardiovasc.Pharmacol. 37:607-618) and in rabbit Purkinje fibers (Lu *et al.* 2002 Europ.J.Pharmacol. 452:183-192).

[00245] Representative compounds of the invention were tested in the Rat Cholesterol Absorption model above. The compounds of the invention exhibited inhibition as shown below in Tables 1a and 1b. The compounds of the invention exhibited ED_{50} values in the rat cholesterol absorption model as shown in Table 2a. Compounds of the invention exhibited ED_{50} values in the mouse and hamster (3 hour and 7 day) cholesterol absorption models (described above) in Table 2b. In some cases, the ED_{50} was calculated in one or more separate experiments. For comparison, Tables 2a and b also show the ED_{50} value for the known cholesterol absorption inhibitor molecule, (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one, in these assays.

Table 1a



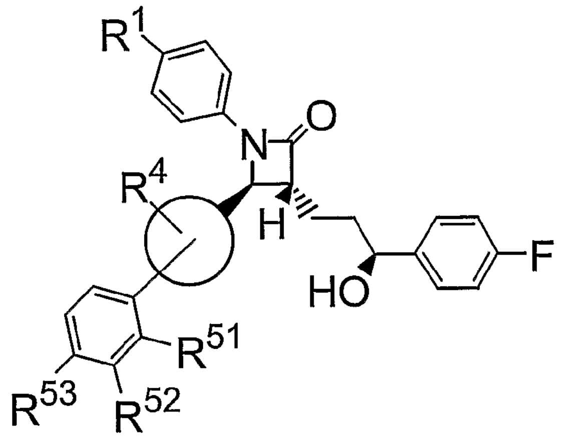
Example #	R^{51}	R^{52}	R^{53}	R^{54}	R^{55}	% inhibition at 1 mg/kg
2			OH			54[1]
3						15[1]
4		OH				72
5			OMe			26[1]
7	OH					30
8			SO_2Me			53
9		OMe	OMe	OMe		40
10		SO_2Me				54[2]
11	OMe	OMe				28
12		OMe				70
13		CHO				70
14		CN				32[3]
15			SO_2NMe_2			8
16		CH_2OH				72
17			NMe_2			43
18			CH_2OH			48
19		OH			Br	66
20		O-glucuronide				59
21		CO_2H				68
22			CO_2H			52
23		NO_2				54[1]
26		NHAc				76[1]
28			NH_2			56
56		$P{=}O(OH)_2$				59
76		O-C6-				56

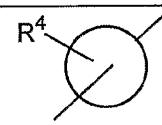
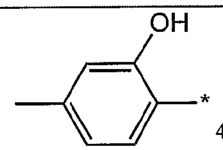
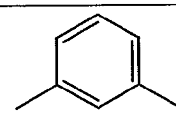
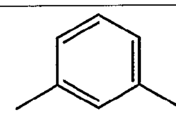
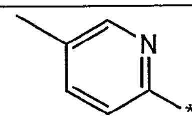
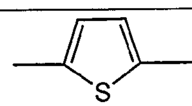
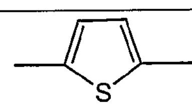
[1] % inhibition at 10 mg/kg
[2] % inhibition at 3 mg/kg
[3] % inhibition at 5 mg/kg

Example #	R^{51}	R^{52}	R^{53}	R^{54}	R^{55}	% inhibition at 1 mg/kg
		glucopyranose				
77		O-C6-methyl glucopyranoside				70
78		O-C6-glucitol				51
81		OMe	OMe			17
82		SMe				28
83		NMe2				38
84			$CH=CH_2$			51
85		OMe			CHO	15
86		NH_2				35
87		$O-CH_2-CH_2-O$				59
88			CH_2CO_2H			30
89			CO_2Me			45
90		Me		Me		27
91		β-naphthyl				56
92		CF_3				17
93		Me				28
94		Me	F			30
95		O-glucopyranose				57
96	OMe	OMe	OMe			69
97	OMe		OMe			40
98	Me					7
99			CHO			38
100		OEt				54
101			OEt			41
102		OMe	OH			56
103		O-nPr				21

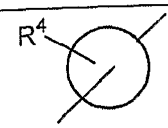
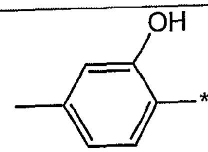
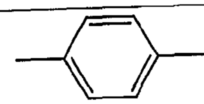
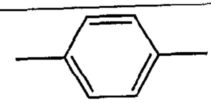
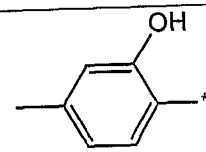
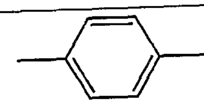
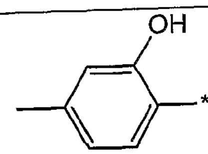
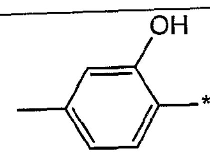
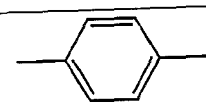
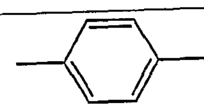
Example #	R^{51}	R^{52}	R^{53}	R^{54}	R^{55}	% inhibition at 1 mg/kg
104		OH			CHO	52
105		O-iPr				15
106		CO_2H	OH			66
107		OMe		OMe		49
108	OH		OH			69
109		O-nBu				52
110		OH	CO_2H			72
111		OMe		F		72
112		OH		F		75
113		C1-glucitol				67
114		OH		OH		72
115		$B(OH)_2$				70
116			C1-gluco pyranose			81
117		C1-CH_2-glucopyranose				26
118		SO_3H				61
119		SH				56
120		NMe_3^+				23
129			F			0
130	F			F		0

Table 1b

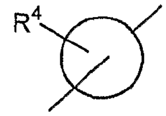
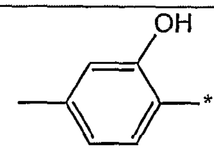
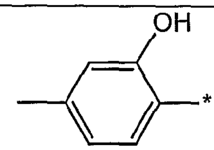
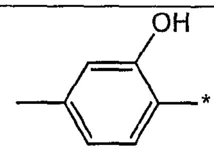
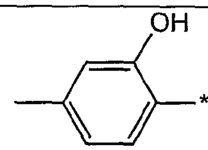
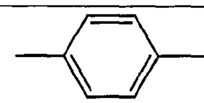
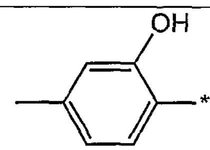
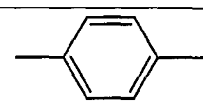
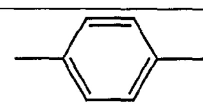
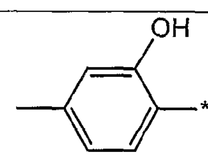


Example #	R^{51}	R^{52}	R^{53}	R^1		% inhibition at 1 mg/kg
42		OH		H		87
44		OH		F		24
46			OH	F		30
49		OH		H		30
50		OH		H		27
51			OH	H		39

[4] The asterix indicates the point of attachment to the azetidine ring.

Exampl e #	R^{51}	R^{52}	R^{53}	R^1		% inhibition at 1 mg/kg
53		SO_3H		H		78
57		OH		H		73
59		$B(OH)_2$		H		70
61		$P{=}O(OH)_2$		H		58[3]
64		C1-glucitol		H		67
65		C1-glucitol		H		60[5]
66			C1-glucitol	H		71[6]
71		C6-S-glucopyranose		H		65
72		C6-R-glucopyranose		H		27[6]

[5] % inhibition at 0.1 mg/kg
[6] % inhibition at 0.3 mg/kg

Example #	R^{51}	R^{52}	R^{53}	R^{1}		% inhibition at 1 mg/kg
73		C6-S-glucopyranose		H		59
74		C6-R-glucopyranose		H		67
75		C6-S-glucitol		H		68
121		OH		F	 [7]	72
122		$P{=}O(OH)_2$		H		67
123		SO_2Me		H		72
124		OH		Ph		48
125			OH	H		64
127			$P{=}O(OH)_2$	H		58

[7] the asterisk indicates the point of attachment to the azetidine ring

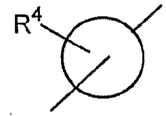
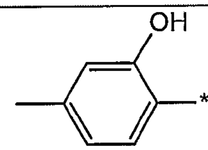
Example #	R^{51}	R^{52}	R^{53}	R^{1}		% inhibition at 1 mg/kg
128			SO_3^- Na^+			60

Table 2A

Row	Name	Rat Acute ED_{50} (mg/kg)
1	(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one	0.002
2	(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-hydroxybiphenyl-4-yl)azetidin-2-one	0.04
3	(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[4'-(methylsulfonyl)biphenyl-4-yl]azetidin-2-one	0.9
4	(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-methoxybiphenyl-4-yl)azetidin-2-one	0.2
5	(3R,4S)-4-(2'-bromo-5'-hydroxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one	0.15
6	4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl β-L-glucopyranosiduronic acid	0.85
7	4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-carbaldehyde	0.25
8	(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[3'-(hydroxymethyl)biphenyl-4-yl]azetidin-2-one	0.25
9	4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-carboxylic acid	0.2
10	4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-4-carboxylic acid	0.3
11	(3R,4S)-4-(2',3'-difluorobiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one	0.2
12	(3R,4S)-4-(4'-aminobiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one	1
13	(3R,4S)-4-[4'-(dimethylamino)biphenyl-4-yl]-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one	>1
14	(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4'-vinylbiphenyl-4-yl)azetidin-2-one	1
15	(3R,4S)-4-(2',4'-difluorobiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one	1

16	(3R,4S)-4-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one	0.3
17	(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-4-yl)acetic acid	>1
18	methyl 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-4-carboxylate	1
19	(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[4-(2-naphthyl)phenyl]azetidin-2-one	0.6
20	(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(2',3',4'-trimethoxybiphenyl-4-yl)azetidin-2-one	0.6
21	(3R,4S)-4-(3'-ethoxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one	0.3
22	(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4'-hydroxy-3'-methoxybiphenyl-4-yl)azetidin-2-one	0.4
23	4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-5-hydroxybiphenyl-2-carbaldehyde	1
24	4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-4-hydroxybiphenyl-3-carboxylic acid	0.3
25	(3R,4S)-4-(3',5'-dimethoxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one	0.3
26	(3R,4S)-4-(2',4'-dihydroxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one	0.03
27	(3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one	0.01
28	(3R,4S)-4-(3'-fluoro-5'-methoxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one	0.03
29	(3R,4S)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-hydroxybiphenyl-4-yl)-1-phenylazetidin-2-one	0.01
30	(3R,4S)-4-(3'-fluoro-5'-hydroxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one	0.2
31	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)-L-glucitol	0.3
32	(3R,4S)-4-(3',5'-dihydroxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one	0.03
33	(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)phosphonic acid	0.5
34	methyl 6-O-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)-α-D-glucopyranoside	0.3
35	(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)boronic acid	0.1

36	(1R)-1,5-anhydro-1-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-4-yl)-L-glucitol	0.1
37	6-O-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)-D-glucopyranose	0.5
38	(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)phosphonic acid	0.5
39	(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)boronic acid	0.3
40	(3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one	0.002
41	4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-sulfonic acid	0.3
42	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)-D-glucitol	0.1
43	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucitol	0.003, 0.01
44	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol	0.008
45	4'-{(2S,3R)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-sulfonic acid	0.1
46	(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)phosphonic acid	0.01
47	(3R,4S)-4-(3,4'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one	0.03
48	(6R)-6-C-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucopyranose	0.03
49	(6S)-6-C-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucopyranose	0.1
50	(6S)-6-C-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucitol	0.03
51	(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid	0.03, 0.001
52	4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-sulfonic acid	0.003, 0.007

Table 2B

Row	*in vivo* model	compound	ED50 (mg/kg)
1	mouse	(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one	0.3
2	mouse	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol	0.3
3	mouse	(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid	0.2
4	mouse	(3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one	0.4
5	mouse	4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-sulfonic acid	0.3
6	hamster (3 hour)	(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one	0.003
7	hamster (3 hour)	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol	0.005
8	hamster (3 hour)	(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid	0.001
9	hamster (3 hour)	(3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one	0.003

10	hamster (7 day)	(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one	0.04 (+/- 0.01), 0.03 (+/- 0.01), 0.03 (+/- 0.01)
11	hamster (7 day)	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol	0.02 (+/- 0.01), 0.03 (+/- 0.01)
12	hamster (7 day)	(3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one	0.02 (+/- 0.01)
13	hamster (7 day)	(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid	0.02
14	hamster (7 day)	4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-sulfonic acid	0.03

Additivity Assay

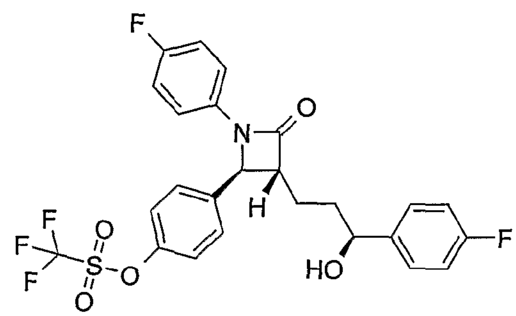
[00246] The effects of three compounds of the invention ((1) (1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol, (2) (3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one, and (3) (4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid) either alone and in combination with the known cholesterol absorption inhibitor, (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one were studied in the rat cholesterol absorption model above. Groups of five rats received each of the three compounds alone (1 mg/kg) or in combination with (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one (each at 1mg/kg) or vehicle (olive oil) via oral gavage. Serum radioactivity (DPM) was measured and the average values are plotted in figures 5A, B, and C.

*In general, the compounds of the present invention may be prepared by the methods illustrated in the general reaction schemes as, for example, described below, or by modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants that are in themselves known, but are not mentioned here.

[00247] The starting materials, in the case of suitably substituted azetidinones, may be obtained by the methods described in WO 02/50027, WO 97/16424, WO 95/26334, WO 95/08532 and WO 93/02048, the disclosures of which are incorporated herein by reference.

[00248] Processes for obtaining the compounds of the invention are presented below. Although detailed syntheses are not presented for every example in Tables 1 and 2, the procedures below illustrate the methods. The other compounds were made in analogous fashion to those whose synthesis is exemplified.

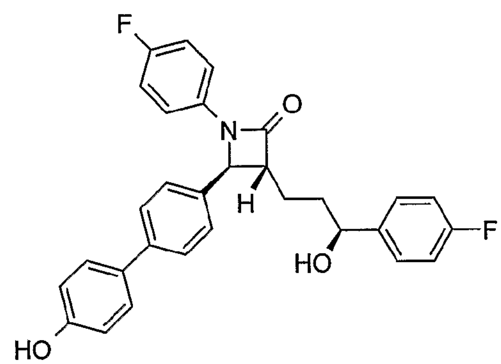
[00249] Example 1. Preparation of the intermediate 4-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}phenyl trifluoromethanesulfonate



[00250] (3R,4S)-1-(4-Fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one (150.4 mg, 0.367 mmol) and 4-dimethylaminopyridine (9.4 mg, 0.077 mmol) were dissolved in methylene chloride (10.0 mL). Triethylamine (100 μL, 72.6 mg, 0.717 mmol) was added via syringe followed by N-phenyltrifluoromethanesulfonimide (143.6 mg, 0.402 mmol) added as a solid. The reaction was stirred for 3.5 h at room temperature and then poured into water (40 mL) and extracted with 1:1 ethyl acetate-hexane (75 mL). The organic layer was washed with water (40 mL) and brine (40 mL), then dried over sodium sulfate,

filtered, concentrated and purified by chromatography (12 g silica gel, 10% to 90% ethyl acetate-hexane) to afford 4-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}phenyl trifluoromethanesulfonate (190.8 mg, 96% yield) as a clear film (eventually becomes a while solid); mp 121.6 °C; R_f 0.38 (2:3 ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, J = 8.7 Hz, 2H), 7.31-7.26 (m, 4H), 7.19 (dd, J = 9.0, 4.6 Hz, 2H), 7.01 (t, J = 8.7 Hz, 2H), 6.95 (t, J = 8.7 Hz, 2H), 4.71 (t, J = 6.0 Hz, 1H), 4.67 (d, J = 2.3 Hz, 1H), 3.10-3.04 (m, 1H), 2.08-1.86 (m, 4H) ppm; MS [M-OH] 524.5.

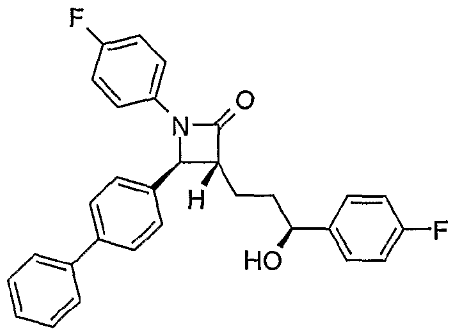
[00251] Example 2. Preparation of (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4'-hydroxybiphenyl-4yl)azetidin-2-one



4-{(2S,3R)-1-(4-Fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}phenyl trifluoromethanesulfonate (162.5 mg, 0.30 mmol) and tetrakis(triphenylphosphine)palladium(0) (17.3 mg, 0.015 mmol) were dissolved in toluene (2.5 mL). 2.0 M aqueous potassium carbonate (0.3 mL) and a solution of 4-hydroxyphenylboronic acid (57.9 mg, 0.42 mmol) in ethanol (1.0 mL) were added. The reaction was stirred vigorously for 5 h at refluxing temperature under a nitrogen atmosphere and then diluted with water (2.5 mL), extracted with ethyl acetate (3 x 10 mL), washed with brine (10 mL), dried over sodium sulfate, filtered, concentrated and purified by chromatography (12 g silica gel, 10% to 100% ethyl acetate-hexane) to afford (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4'-hydroxybiphenyl-4-yl)azetidin-2-one (112 mg, 77% yield) as a clear film; mp 110 °C; R_f 0.5 (1:1 ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5 (d, J = 9.0 Hz, 2H) 7.4 (d, J = 9.0 Hz, 2H) 7.3 (m, 6H), 6.9 (m, 6H), 4.7 (m, 1H), 4.6 (s, 1H), 3.15 (m, 1H), 2.1-1.9 (m, 4H) ppm; MS [M+H] 486.5.

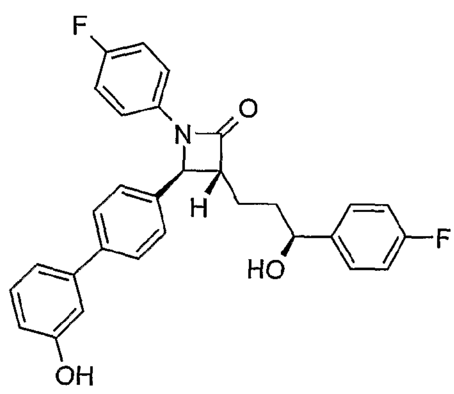
In the same manner was obtained:

[00252] Example 3. (3R,4S)-4-Biphenyl-4-yl-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one



(3R,4S)-4-Biphenyl-4-yl-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one (11.8 mg, 54% yield) as a clear film; purification by chromatography (4 g silica gel, 10% to 100% ethyl acetate-hexane) and then by reverse-phase HPLC (21mm column, 50% to 100% acetonitrile-0.1% trifluoroacetic acid in water); R_f 0.47 (3:2 ethyl acetate-hexane); ^{1}H NMR (300 MHz, CD_3OD) δ 7.63 (d, J = 8.3 Hz, 2H), 7.61-7.58 (m, 2H), 7.45-7.39 (m, 4H), 7.35-7.28 (m, 5H), 7.02 (t, J = 8.8 Hz, 2H), 7.00 (t, J = 8.8 Hz, 2H), 4.63 (t, J = 5.7 Hz, 1H), 3.15-3.00 (m, 1H), 2.05-1.84 (m, 5H) ppm; MS [M-OH] 452.5

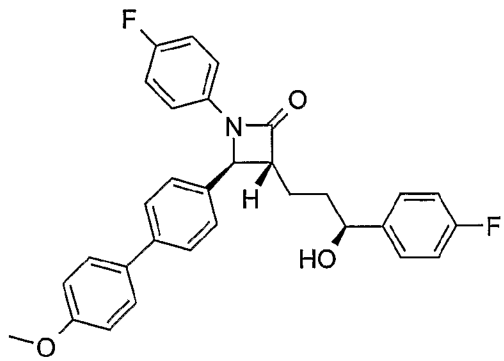
[00253] Example 4. (3R,4S)-1-(4-Fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-hydroxybiphenyl-4-yl)azetidin-2-one



(3R,4S)-1-(4-Fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-hydroxybiphenyl-4-yl)azetidin-2-one (110 mg, 76% yield using a reaction time of 4 h) as an off white solid; purification by chromatography (12 g silica gel, 10% to 100%

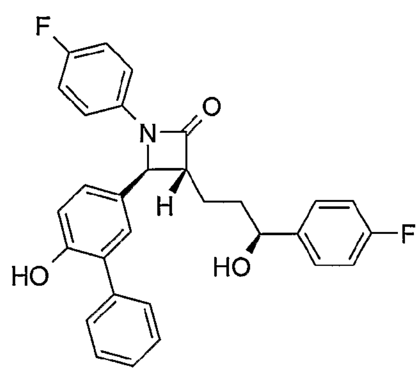
ethyl acetate-hexane); mp 107 °C; R_f 0.50 (1:1 ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6 (d, J = 8.9 Hz, 2H), 7.3 (d, J = 8.9 Hz, 2H), 7.2 (m, 6H), 6.9 (m, 6H), 4.7(m, 1H), 4.6(s, 1H), 3.15 (m, 1H), 2.1-1.9 (m, 4H) ppm; MS [M+H] 486.5

[00254] Example 5. (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4'-methoxybiphenyl-4-yl)azetidin-2-one



(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4'-methoxybiphenyl-4-yl)azetidin-2-one (86 mg, 67% yield using a reaction time of 16 h) as a white solid; purification by chromatography (12 g silica gel, 10% to 100% ethyl acetate-hexane); mp 103 °C; R_f 0.75 (1:1 ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 (m, 4H), 7.3 (m, 6H), 6.9 (m, 6H), 4.75 (m, 1H), 4.65 (s, 1H), 3.85 (s, 3H), 3.2 (m, 1H), 2.1-1.9 (m, 4H) ppm; MS [M-OH] 482.5

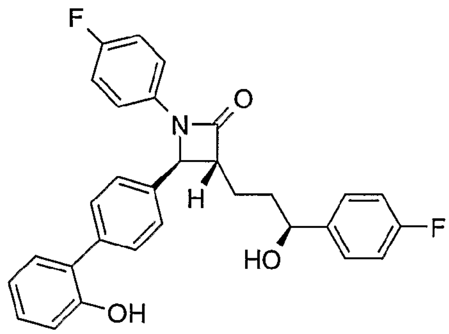
[00255] Example 6. (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(6-hydroxybiphenyl-3-yl)azetidin-2-one



(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(6-hydroxybiphenyl-3-yl)azetidin-2-one (36 mg, 40% yield using a reaction time of 16 h) as a white solid; purification by chromatography (12 g silica gel, 10% to 100% ethyl acetate-hexane); mp 113 °C; R_f 0.70 (1:1 ethyl acetate-hexane); ^{1}H NMR (300 MHz,

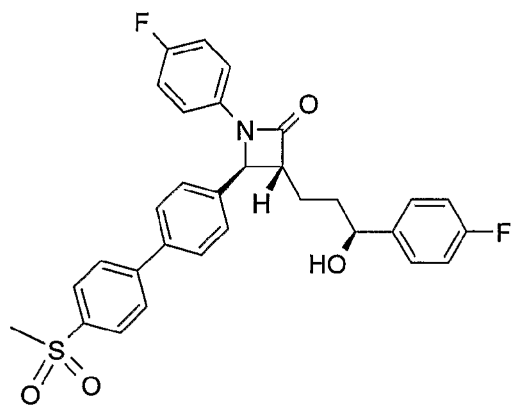
$CDCl_3$) δ 7.5-6.9 (m, 16H), 4.75 (m, 1H), 4.65 (s, 1H), 3.2 (m, 1H), 2.1-1.9 (m, 4H) ppm; MS [M+H] 486.5

[00256] Example 7. (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(2'-hydroxybiphenyl-4-yl)azetidin-2-one



(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(2'-hydroxybiphenyl-4-yl)azetidin-2-one (74 mg, 51% yield using a reaction time of 2 h) as a white solid; purification by chromatography (12 g silica gel, 10% to 100% ethyl acetate-hexane); mp 101 °C; R_f 0.50 (1:1 ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6 (d, J = 9.0 Hz, 2H), 7.4 (d, J = 9.0 Hz, 2H), 7.25 (m, 6H), 6.9 (m, 6H), 6.3 (s, 1H), 4.65 (m, 2H), 3.1 (m, 1H), 2.1-1.9 (m, 4H) ppm; MS [M+H] 486.5

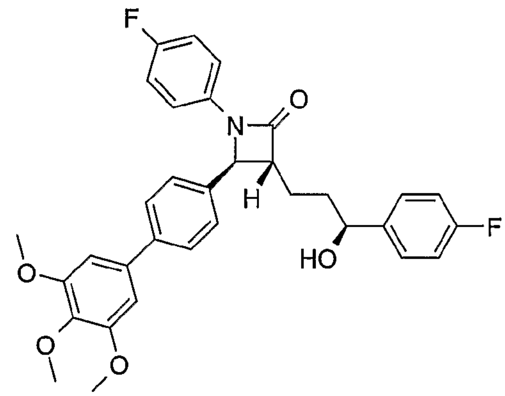
[00257] Example 8. (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[4'-(methylsulfonyl)biphenyl-4-yl]azetidin-2-one



(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[4'-(methylsulfonyl)biphenyl-4-yl]azetidin-2-one (80 mg, 79% yield using a reaction time of 4 h) as a white solid; purification by chromatography (12 g silica gel, 10% to 100% ethyl acetate-hexane); mp 111°C; R_f 0.40 (1:1 ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.1 (d, J = 9.3 Hz, 2H), 7.8 (d, J = 9.3 Hz, 2H), 7.6 (d, J = 8.1 Hz,

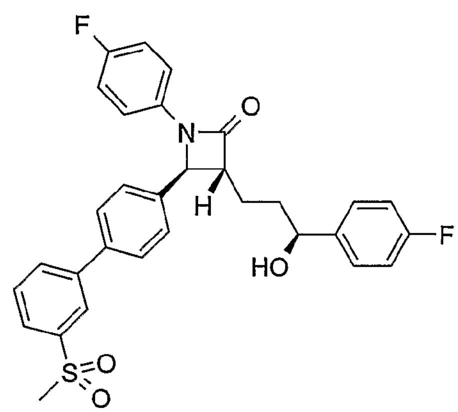
2H), 7.5 (d, J = 8.1 Hz, 2H), 7.3 (m, 5H), 6.9 (m, 3H), 6.3 (s, 1H), 4.7 (m, 1H), 4.6 (s, 1H), 3.1 (s, 4H), 2.1-1.9 (m, 4H) ppm; MS [M-OH] 530.6

[00258] Example 9. (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3',4',5'-trimethoxybiphenyl-4-yl)azetidin-2-one



(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3',4',5'-trimethoxybiphenyl-4-yl)azetidin-2-one (93 mg, 90% yield using a reaction time of 2 h) as a white solid; purification by chromatography (12 g silica gel, 10% to 100% ethyl acetate-hexane); mp 103 °C; R_f 0.4 (1:1 ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6 (d, J = 9.0 Hz, 2H), 7.5 (d, J = 9.0 Hz, 2H), 7.3 (m, 4H), 7.0 (m, 4H), 6.8 (s, 2H), 4.7 (m, 1H), 4.6 (s, 1H), 3.9 (s, 9H), 3.1 (s, 1H), 2.1-1.9 (m, 4H) ppm; MS [M-OH] 542.6

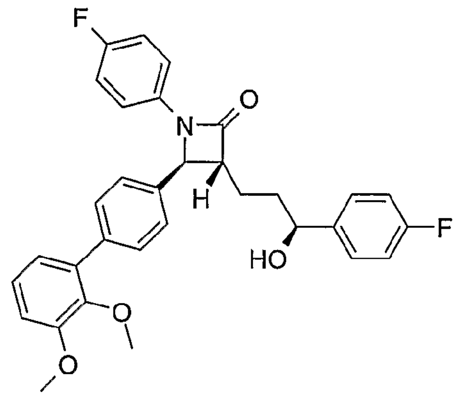
[00259] Example 10. (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[3'-(methylsulfonyl)biphenyl-4-yl]azetidin-2-one



(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[3'-(methylsulfonyl)biphenyl-4-yl]azetidin-2-one (92 mg, 90% yield using a reaction time of 2 h) as a white solid; purification by chromatography (12 g silica gel, 10% to 100%

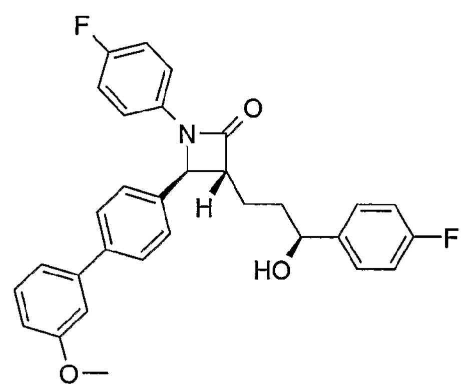
ethyl acetate-hexane); mp 104 °C; R_f 0.45 (1:1 ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.2-6.8 (m, 15H), 4.7 (m, 1H), 4.65 (s, 1H), 3.2 (m, 1H), 3.1 (s, 3H), 2.1-1.9 (m, 4H) ppm; MS [M-OH] 530.6

[00260] Example 11. (3R,4S)-4-(2',3'-dimethoxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one



(3R,4S)-4-(2',3'-dimethoxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one (132.0 mg, 90% yield using a reaction time of 2 h) as a white solid; purification by chromatography (12 g silica gel, 10% to 100% ethyl acetate-hexane); mp 101 °C; R_f 0.70 (1:1 ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6 (d, J = 8.5 Hz, 2H), 7.4 (d, J = 8.5 Hz, 2H), 7.3 (m, 5H), 7.0 (m, 6H), 4.7 (m, 1H), 4.6 (s, 1H), 3.9 (s, 3H), 3.7 (s, 3H), 3.3 (m, 1H), 2.1-1.9 (m, 4H) ppm; MS [M-OH] 512.6

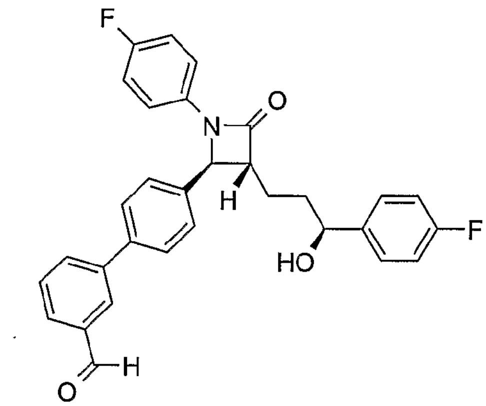
[00261] Example 12. (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-methoxybiphenyl-4-yl)azetidin-2-one



(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-methoxybiphenyl-4-yl)azetidin-2-one (36.1 mg, 77% yield) as a clear foam;

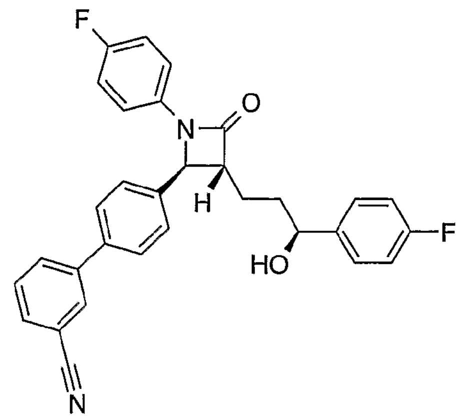
purification by chromatography (12 g silica gel, 5% to 95% ethyl acetate-hexane); R_f 0.52 (40% ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 8.7 Hz, 2H), 7.30 (m, 7H), 7.15 (dt, J = 13.5, 1.5 Hz, 1H), 7.09 (t, J = 2.4 Hz, 1H), 7.00 (t, J = 10.4 Hz, 2H), 6.92 (m, 3H), 4.73 (t, J = 6.2 Hz, 1H), 4.67 (d, J = 2.1 Hz, 1H), 3.86 (s, 3H), 1.95 (m, 4H); MS [M-OH] 482.5

[00262] Example 13. 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-carbaldehyde



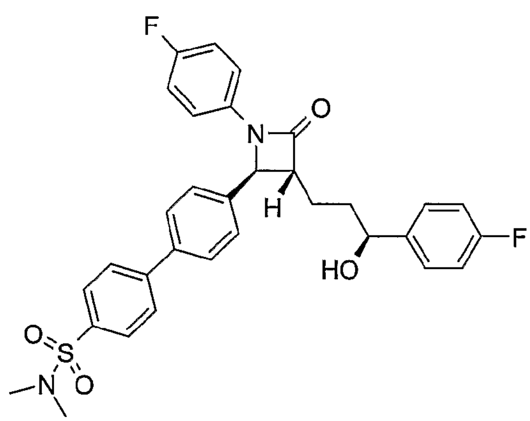
4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-carbaldehyde (32.7 mg, 67% yield) as a clear foam; purification by chromatography (12 g silica gel, 5% to 95% ethyl acetate-hexane); R_f 0.72 (50% ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.09 (s, 1H), 8.09 (d, J = 1.8 Hz, 1H), 7.85 (m, 2H), 7.62 (m, 3H), 7.44 (d, J = 7.8 Hz, 2H), 7.27 (m, 4H), 7.03 (t, J = 8.6 Hz, 2H), 6.95 (t, J = 8.8 Hz, 2H), 4.74 (m, 1H), 4.70 (d, J = 2.4 Hz, 1H), 3.14 (m, 1H), 1.97 (m, 4H) ppm; MS [M-OH] 480.5

[00263] Example 14. 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-carbonitrile



4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-carbonitrile (32.5 mg, 57% yield) as a clear foam; purification by chromatography (12 g silica gel, 5% to 95% ethyl acetate-hexane); R_f 0.69 (50% ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (m, 1H), 7.79 (m, 1H), 7.64 (m, 1H), 7.55 (m, 3H), 7.44 (d, J = 6.6 Hz, 2H), 7.28 (m, 4H), 7.02 (t, J = 8.9 Hz, 2H), 6.95 (t, J = 8.9 Hz, 2H), 4.75 (t, J = 6.2 Hz, 1H), 4.68 (d, J = 2.1 Hz, 1H), 3.13 (m, 1H), 2.01 (m, 4H) ppm; MS [M-OH] 477.5

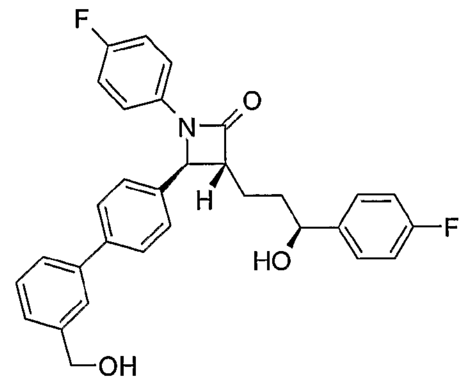
[00264] Example 15. 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-N,N-dimethylbiphenyl-4-sulfonamide



4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-N,N-dimethylbiphenyl-4-sulfonamide (39.6 mg, 73% yield) as a faint yellow foam; purification by chromatography (12 g silica gel, 5% to 95% ethyl acetate-hexane); R_f 0.50 (50% ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 5.4 Hz, 2H), 7.72 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.25 (m, 4H), 7.02 (t, J = 8.4, 9.0 Hz, 2H), 6.95 (t, J = 8.7

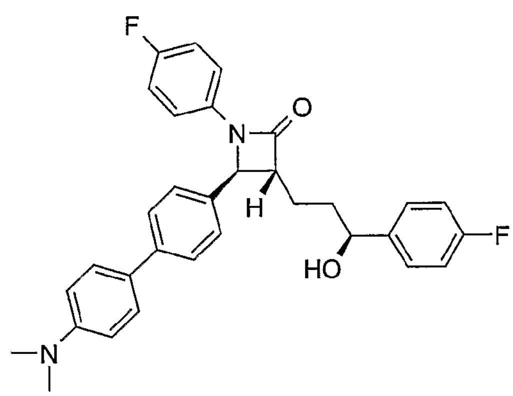
Hz, 2H), 4.74 (t, J = 5.5 Hz, 1H), 4.69 (d, J = 1.8 Hz, 1H), 3.13 (m, 1H), 2.75 (s, 6H), 2.01 (m, 4H) ppm; MS [M-OH] 559.7

[00265] Example 16. (3R,4S)-1-(4-Fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-(hydroxymethyl)biphenyl-4-yl)azetidin-2-one



(3R,4S)-1-(4-Fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-(hydroxymethyl)biphenyl-4-yl)azetidin-2-one (37.3 mg, 80% yield) as a clear foam; purification by chromatography (12 g silica gel, 5% to 95% ethyl acetate-hexane); R_f 0.43 (50% ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (m, 3H), 7.49 (m, 2H), 7.37 (m, 3H), 7.27 (m, 4H), 7.02 (t, J = 8.7 Hz, 2H), 6.95 (t, J = 8.7 Hz, 2H), 4.74 (m, 1H), 4.67 (d, J = 2.4 Hz, 1H), 3.14 (m, 1H), 1.99 (m, 4H) ppm; MS [M-OH] 482.5

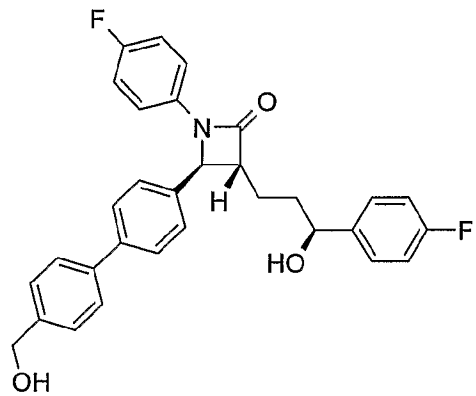
[00266] Example 17. (3R,4S)-4-[4'(dimethylamino)biphenyl-4-yl]-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one



(3R,4S)-4-[4'(dimethylamino)biphenyl-4-yl]-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one (35.4 mg, 79% yield) as a white foam; purification by chromatography (12 g silica gel, 5% to 95% ethyl acetate-hexane); R_f

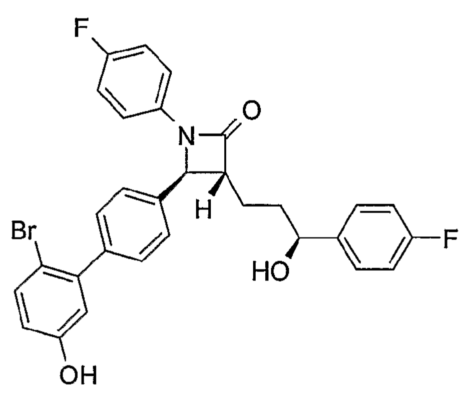
0.78 (50% ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (m, 4H), 7.31 (m, 8H), 7.02 (t, J = 8.7 Hz, 2H), 6.94 (t, J = 8.7 Hz, 2H), 4.73 (m, 1H), 4.64 (d, J = 2.1 Hz, 1H), 3.14 (m, 1H), 3.10 (s, 6H) 1.97 (m, 4H) ppm; MS [M+H] 513.6

[00267] Example 18. (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[4-(hydroxymethyl)phenyl]azetidin-2-one



(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[4-(hydroxymethyl)phenyl]azetidin-2-one (37.2 mg, 75% yield with a 7% impurity) as a clear film; purification by chromatography (12 g silica gel, 5% to 95% ethyl acetate-hexane); R_f 0.43 (50% ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (m, 4H), 7.44 (d, J = 8.4, 2H), 7.38 (d, J = 8.4, 2H), 7.27 (m, 4H), 7.02 (t, J = 8.9 Hz, 2H), 6.95 (t, J = 8.7 Hz, 2H), 4.73 (m, 3H), 4.66 (d, J = 2.4 Hz, 1H), 3.12 (m, 1H), 1.97 (m, 4H) ppm; MS [M-OH] 482.5

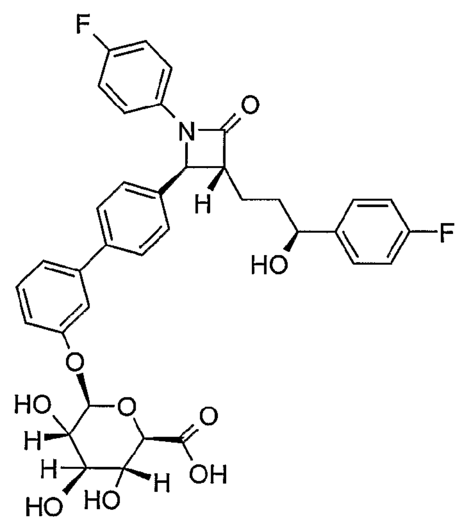
[00268] Example 19. Preparation of (3R,4S)-4-(2'-bromo-5'-hydroxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one



(3R,4S)-1-(4-Fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-hydroxybiphenyl-4-yl)azetidin-2-one (19.2 mg, 0.04 mmol) was dissolved in

chloroform (0.4 mL) and tetrabutylammonium tribromide (18.8 mg, 0.04 mmol) was added at room temperature. After 10 minutes, saturated aqueous sodium thiosulfate (2 mL) was added to quench the reaction. The mixture was poured into a seperatory funnel, extracted with dichloromethane (4 x 10 mL), dried over sodium sulfate, filtered and concentrated. (3R,4S)-4-(2'-bromo-5'-hydroxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one was purified by chromatography (12 g silica gel, 5% to 95% ethyl acetate-hexane) and then by reverse-phase HPLC (21mm column, 50% to 100% acetonitrile-0.1% trifluoroacetic acid in water) to afford (3R,4S)-4-(2'-bromo-5'-hydroxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one (8.0 mg, 34% yield) as a clear foam; R_f 0.51 (50% ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, J = 8.7 Hz, 1H), 7.40 (m, 4H), 7.29 (m, 4H), 7.02 (t, J = 8.7 Hz, 2H), 6.95 (t, J = 8.7 Hz, 2H), 6.80 (d, J = 3.3, 1H), 6.73 (dd, J = 3.0, 3.0 Hz, 1H), 4.74 (t, J = 6.2 Hz, 2H), 4.67 (d, J = 2.1 Hz, 1H), 3.14 (m, 1H) 1.99 (m, 4H) ppm; MS [M-OH] 547.4

[00269] Example 20. Preparation of 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl β-L-glucopyranosiduronic acid



[00270] Step 1: Preparation of (1S)-1-(4-fluorophenyl)-3-[(3R,4S)-1-(4-fluorophenyl)-2-oxo-4-(4-{[(trifluoromethyl)sulfonyl]oxy}-phenyl)azetidin-3-yl]propyl acetate

[00271] 4-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}phenyl trifluoromethanesulfonate (0.16 g, 0.35 mmol) was dissolved in dichloromethane (2 mL). To this was added acetic anhydride (0.04 mL, 0.45 mmol), triethylamine (0.08 mL, 0.60 mmol) and 4-dimethylaminopyridine (18.3 mg, 0.15 mmol). The reaction was stirred at room temperature for 18 h after which time it was diluted with water (5 mL) and extracted with dichloromethane (10 mL). The aqueous layer was re-extracted with dichloromethane (3 x 10 mL) and the organic fractions were combined, dried over sodium sulfate, filtered and concentrated. The residue was purified by chromatography (12 g silica gel, 5% to 95% ethyl acetate-hexane) to afford (1S)-1-(4-fluorophenyl)-3-[(3R,4S)-1-(4-fluorophenyl)-2-oxo-4-(4-[(trifluoromethyl)sulfonyl]oxy}-phenyl)azetidin-3-yl]propyl acetate (0.20 g, 0.35 mmol, 100%) as a clear film.

[00272] Step 2: Preparation of (1S)-1-(4-fluorophenyl)-3-[(2S,3R)-1-(4-fluorophenyl)-2-(3'-hydroxybiphenyl-4-yl)-4-oxoazetidin-3-yl]propyl acetate.

[00273] The product of step 1 (0.20 g, 0.35 mmol) and tetrakis(triphenylphosphine)palladium(0) (20.3 mg, 0.018 mmol) were dissolved in toluene (10 mL). 2.0 M aqueous potassium carbonate (0.35 mL) and a solution of 4-hydroxyphenylboronic acid (67.8 mg, 0.49 mmol) in ethanol (2.5 mL) was added. The reaction was stirred vigorously for 4 h at refluxing temperature under a nitrogen atmosphere and then diluted with water (2.5 mL), extracted with ethyl acetate (3 x 10 mL), washed with brine (10 mL), dried over sodium sulfate, filtered, concentrated and purified by chromatography (12 g silica gel, 5% to 95% ethyl acetate-hexane) to afford (1S)-1-(4-fluorophenyl)-3-[(2S,3R)-1-(4-fluorophenyl)-2-(3'-hydroxybiphenyl-4-yl)-4-oxoazetidin-3-yl]propyl acetate (157 mg, 85% yield) as a clear film.

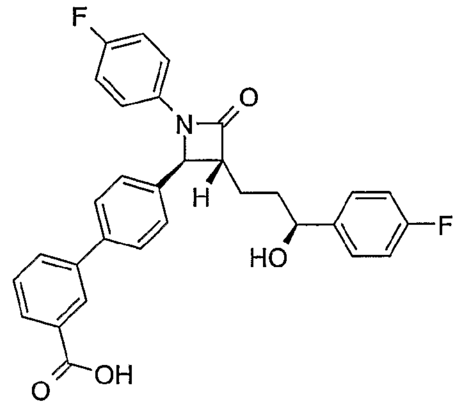
[00274] Step 3: Preparation of (1S)-1-(4-fluorophenyl)-3-((3R,4S)-1-(4-fluorophenyl)-2-oxo-4-{3'-[(2,3,4-tri-O-acetyl-6-hydroperoxy-β-L-gluco-hexodialdo-1,5-pyranosyl)oxy]biphenyl-4-yl}azetidin-3-yl)propyl acetate.

[00275] The product of step 2 (69.4 mg, 0.132 mmol) and methyl 2,3,4-tri-O-acetyl-1-O-(2,2,2-trifluoroethanimidoyl)-D-glucopyranuronate (49.0 mg, 0.110 mmol) were azeotroped with toluene (3 x 15 mL) and dried in vacuo for 18 h. The dried syrup was suspended in dichloromethane (1.1 mL) and the reaction was cooled to –25 °C. Freshly distilled (over calcium hydride) boron trifluoride diethyl etherate was added and the reaction was maintained at -25° C for 2 h and warmed to 10 °C over about 3.5 h. The mixture was diluted with saturated aqueous ammonium chloride (2 mL), extracted with ethyl acetate (3 x 10 mL), washed with brine (10 mL), dried over sodium sulfate, filtered, concentrated and purified by chromatography (12 g silica gel, 5% to 95% ethyl acetate-hexane) to afford (1S)-1-(4-fluorophenyl)-3-((3R,4S)-1-(4-fluorophenyl)-2-oxo-4-{3'-[(2,3,4-tri-O-acetyl-6-hydroperoxy-β-L-gluco-hexodialdo-1,5-pyranosyl)oxy]biphenyl-4-yl}azetidin-3-yl)propyl acetate (57.2 mg, 87% based on recovered starting material) as a white foam.

[00276] Step 4: Preparation of 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl β-L-glucopyranosiduronic acid.

[00277] The product of step 3 (57.2 mg, 0.068 mmol) was dissolved in 1:1 methanol-triethylamine (2.8 mL). To this solution was added water (4.25 mL). The reaction progress was monitored by TLC (5% acetic acid and 15% methanol in dichloromethane) and was complete after 19 hours. The methanol and triethylamine were evaporated in vacuo, the residue was acidified with 1 N aqueous hydrochloric acid (1.4 mL), extracted with ethyl acetate (20 mL), washed with brine (5 mL), dried over sodium sulfate, filtered, concentrated and purified by chromatography (10 g silica gel, 5% acetic acid and 15% methanol in dichloromethane) to afford 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl β-L-glucopyranosiduronic acid (32.6 mg, 73%) as an off-white foam; R_f 0.37 (5% acetic acid and 15% methanol in dichloromethane); ^{1}H NMR (300 MHz, CD_3OD) δ 7.63 (d, J = 7.8 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 7.33 (m, 7H), 7.06 (m, 5H), 5.03 (m, 1H), 4.63 (t, J = 5.1, 5.1 Hz, 2H), 3.94 (m, 3H), 3.13 (m, 1H) 1.91 (m, 4H) ppm; MS [M-H] 660.6

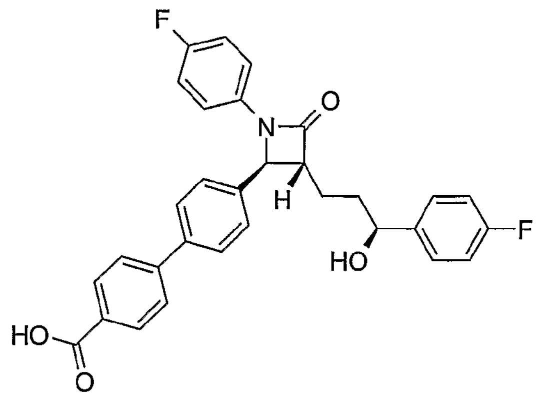
[00278] Example 21. Preparation of 4'-{(2S,3R)-1-(4-fluorophenyl)3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl]biphenyl-3-carboxylic acid



[00279] 4-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}phenyl trifluoromethanesulfonate (51.1 mg, 0.094 mmol) and 3-carboxyphenylboronic acid (21.9 mg, 0.132 mmol) were dissolved in 1:1 toluene:ethanol (2 mL). 2.0 M aqueous potassium carbonate (0.14 mL) was added and the solution degassed. Tetrakis(triphenylphosphine)palladium(0) (5.1 mg, 0.005 mmol) was added and the reaction stirred vigorously for 2 h at refluxing temperature under a nitrogen atmosphere. The cooled reaction was diluted into dichloromethane (15 mL), water (3 mL) was added and the pH was adjusted to 3 with 5% aqueous sodium bisulfate. The layers were separated and the aqueous layer extracted with dichloromethane (2 x 5 mL). The combined organic extracts were dried over sodium sulfate, filtered, concentrated and purified by chromatography (12 g silica gel, 5% methanol in dichloromethane) to afford 4'-{(2S,3R)-1-(4-fluorophenyl)3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl]biphenyl-3-carboxylic acid (41.9 mg, 86% yield) as a colorless foam; R_f 0.15 (5% methanol in dichloromethane); ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (m, 1H), 8.09 (dt, J = 7.8, 1.5 Hz, 1H), 7.79-7.39 (m, 6H), 7.23-7.32 (m, 4H), 6.90-7.02 (m, 4H), 4.75 (t, J = 5.7 Hz, 1H), 4.69 (d, J = 2.1 Hz), 3.12 (m, 1H), 2.10-1.90 (m, 4H) ppm; MS [M-H] 512.5

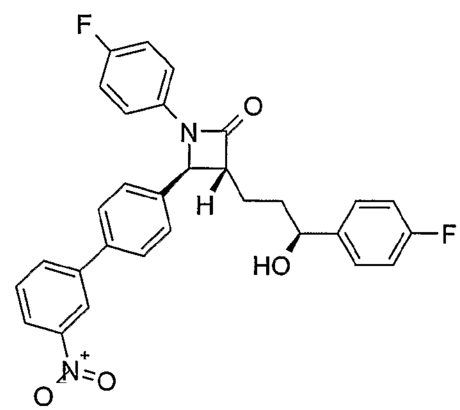
[00280] In the same manner was obtained:

[00281] Example 22. 4'-{(2S,3R)-1-(4-fluorophenyl)3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl]biphenyl-4-carboxylic acid



4'-{(2S,3R)-1-(4-fluorophenyl)3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl]biphenyl-4-carboxylic acid (21.0 mg, 67% yield) as a white foam; purification by chromatography (12 g silica gel, 5% methanol in dichloromethane); R_f 0.14 (5% methanol in dichloromethane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 8.4 Hz, 2H), 7.65 (t, J = 8.1 Hz, 4H), 7.43 (d, J = 8.4 Hz, 2H), 7.33-7.24 (m, 4H), 7.04-6.92 (m, 4H), 4.77 (t, J = 5.7 Hz, 1H), 4.70 (d, J = 2.1 Hz, 1H), 3.15 (m, 1H), 1.92-2.09 (m, 4H) ppm; MS [M-H] 512.5

[00282] Example 23. Preparation of (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-nitrobiphenyl-4-yl)azetidin-2-one

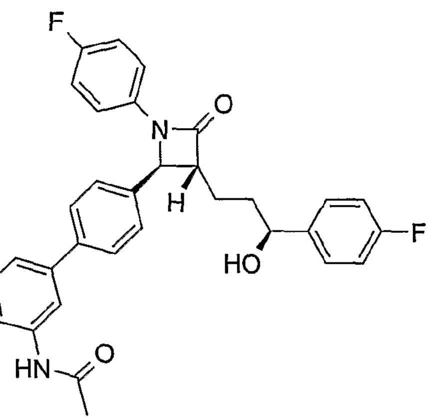


4-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}phenyl trifluoromethanesulfonate (50.0 mg, 0.092 mmol) and 3-nitrophenylboronic acid (21.6 mg, 0.129 mmol) were dissolved in 1:1 toluene:ethanol (2 mL). 2.0 M aqueous potassium carbonate (0.092 mL) was added and the solution degassed. Tetrakis(triphenylphosphine)palladium(0) (5.7 mg, 0.005 mmol) was added and the reaction stirred vigorously for 2 h at refluxing temperature under a nitrogen

atmosphere. The cooled reaction was diluted into dichloromethane (15 mL). The layers were separated and the aqueous layer further extracted with dichloromethane (2 x 5 mL). The combined extracts were dried over sodium sulfate, filtered, concentrated and purified by chromatography (12 g silica gel, 5% to 50% ethyl acetate-hexane) to afford (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-nitrobiphenyl-4-yl)azetidin-2-one (45.0 mg, 95% yield) as a clear film; R_f 0.33 (50% ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (m, 1H), 8.21 (ddd, J = 8.1, 2.4, 1.2 Hz, 1H), 7.89 (ddd, J = 7.9, 1.5, 1.2 Hz, 1H), 7.63 (d, J = 8.1 Hz, 2H), 7.45 (d, J = 8.1 Hz, 2H), 7.33-7.22 (m, 4H), 7.04-6.92 (m, 4H), 4.76 (t, J = 6.0 Hz, 1H), 4.71 (d, J = 2.1 Hz, 1H), 3.14 (m, 1H), 1.91-2.11 (m, 4H) ppm; MS [M-OH] 497.5

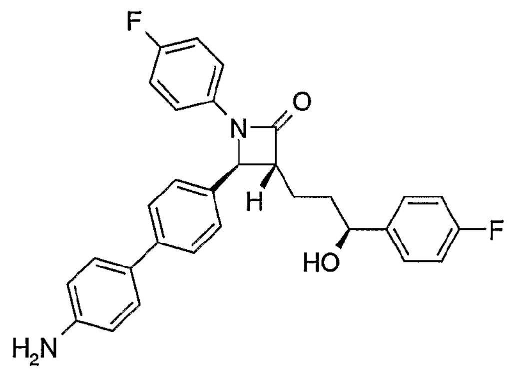
[00283] In the same manner was obtained:

[00284] Example 26. N-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)acetamide



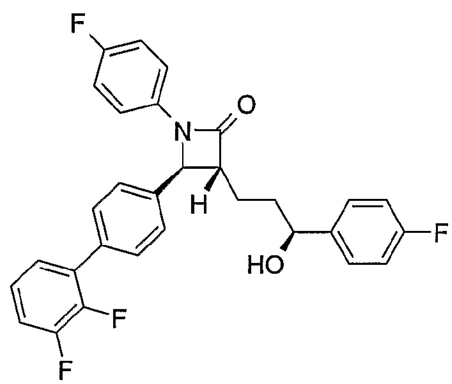
N-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)acetamide (18.8 mg, 44% yield) as a white foam; purification by chromatography (12 g silica gel, 50% ethyl acetate-hexane); R_f 0.07 (50% ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (b, 1H), 7.72-7.19 (m, 12H), 6.99 (t, J = 8.7 Hz, 2H), 6.93 (t, J = 9.0 Hz, 2H), 4.72 (t, J = 5.7 Hz, 1H), 4.65 (d, J = 2.1 Hz, 1H), 3.13 (m, 1H), 2.17 (s, 3H), 2.04-1.88 (m, 4H) ppm; MS [M-OH] 509.6

[00285] Example 28. (3R,4S)-4-(4'-aminobiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl] azetidin-2-one



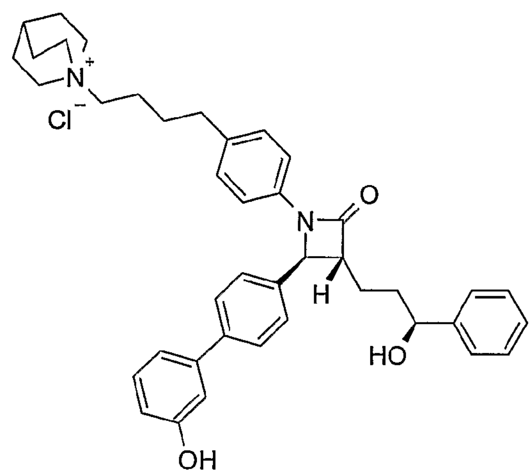
(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4'-aminobiphenyl-4-yl)azetidin-2-one (42.0 mg, 95% yield) as a brown film; purification by chromatography (12 g silica gel, 50% ethyl acetate-hexane); R_f 0.32 (50% ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, J = 8.1 Hz, 2H), 7.39-7.23 (m, 8H), 7.00 (t, J = 8.7 Hz, 2H), 6.92 (t, J = 8.7 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 4.72 (t, J = 5.7 Hz, 1H), 4.63 (d, J = 2.4 Hz, 1H), 3.14 (m, 1H), 2.11-1.91 (m, 4H) ppm; MS [M+H] 485.5

[00286] Example 29. (3R,4S)-1-(2',3'-difluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3',4'-difluorobiphenyl-4-yl)azetidin-2-one



(3R,4S)-1-(2',3'-difluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3',4'-difluorobiphenyl-4-yl)azetidin-2-one (36.9 mg, 86% yield) as a clear film; purification by chromatography (12 g silica gel, 5% to 50% ethyl acetate-hexane); R_f 0.51 (50% ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (dd, J = 8.3, 1.5 Hz, 2H), 7.41 (d, J = 6.9 Hz, 2H), 7.32-7.22 (m, 4H), 7.19-7.12 (m, 3H), 7.01 (t, J = 8.7 Hz, 2H), 6.95 (t, J = 9.0 Hz, 2H), 4.74 (t, J = 6.0 Hz, 1H), 4.68 (d, J = 2.7 Hz, 1H), 3.14 (m, 1H), 2.07-1.90 (m, 4H) ppm; MS [M-OH] 488.5

[00287] Example 31. 1-[4-(4-{(2S,3R)-2-(3'-hydroxybiphenyl-4-yl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-1-yl}phenyl)butyl]-1-azoniabicyclo[2.2.2]octane chloride.

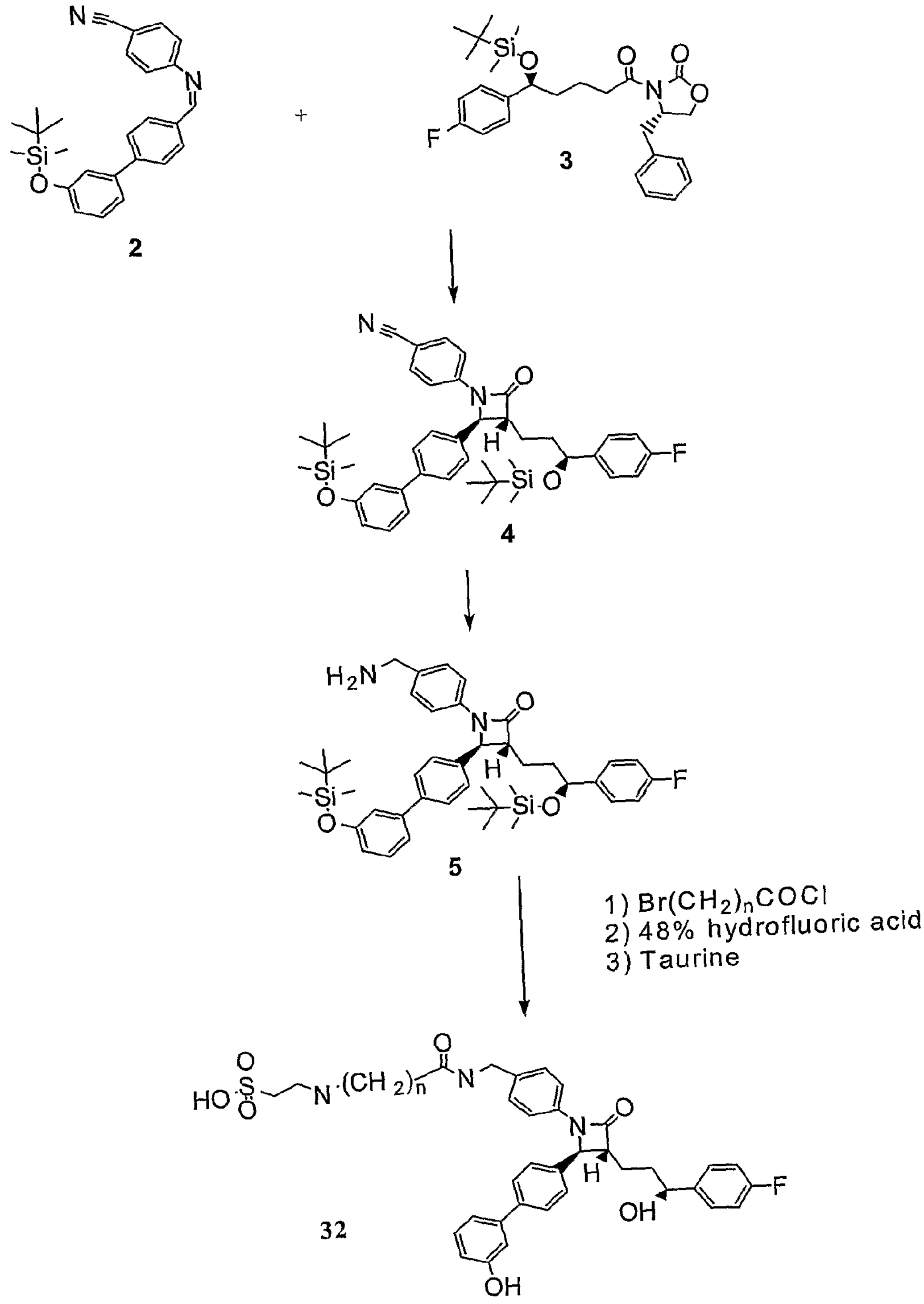


[00288] A quaternary salt is made in the following manner. (3-{[tert-butyl(dimethyl)silyl]oxy}phenyl)boronic acid and 4-bromostyrene are coupled under Suzuki conditions with tetrakis(triphenylphosphine)palladium(0) and 2.0 M aqueous potassium carbonate in toluene-ethanol solvent. The product is reacted with chlorosulfonyl isocyanate in ethereal solvent followed by alkali aqueous work-up to generate a β-lactam. The amide proton is exchanged for an aryl group by reaction with 4-iodophenylcarbonylallyl (generated from the commercially available acid by borane reduction and protected with allyl chloroformate) using trans-1,2-cyclohexanediamine and copper (I) iodide in decane-dioxane as solvent. Deprotonation of the 3-position of the β-lactam with a suitable base, such as lithium diisopropylamide, and subsequent quenching with tert-butyl{[(1S)-4-iodo-1-phenylbutyl]oxy}dimethylsilane (generated from the commercially available (S)-(-)-3-chloro-1-phenyl-1-propanol by protection with tert-butyldimethylchlorosilane and Finkelstein reaction with sodium iodide) provide the 3-substituted intermediate. The allyloxycarbonate protecting group is removed with ammonium formate and tetrakis(triphenylphosphine)palladium(0) in tetrahydrofuran and the resulting alcohol converted into the bromide using carbon tetrabromide and triphenylphosphine in dichloromethane. The silyl protecting groups are removed from the benzyl alcohol

and the phenol using 48% hydrofluoric acid in acetonitrile. The resulting compound is reacted with a tertiary amine, such as quinuclidine, purified by HPLC and passed through a chloride ion-exchange column to afford 1-[4-(4-{(2S,3R)-2-(3'-hydroxybiphenyl-4-yl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-1-yl}phenyl)butyl]-1-azoniabicyclo[2.2.2]octane chloride.

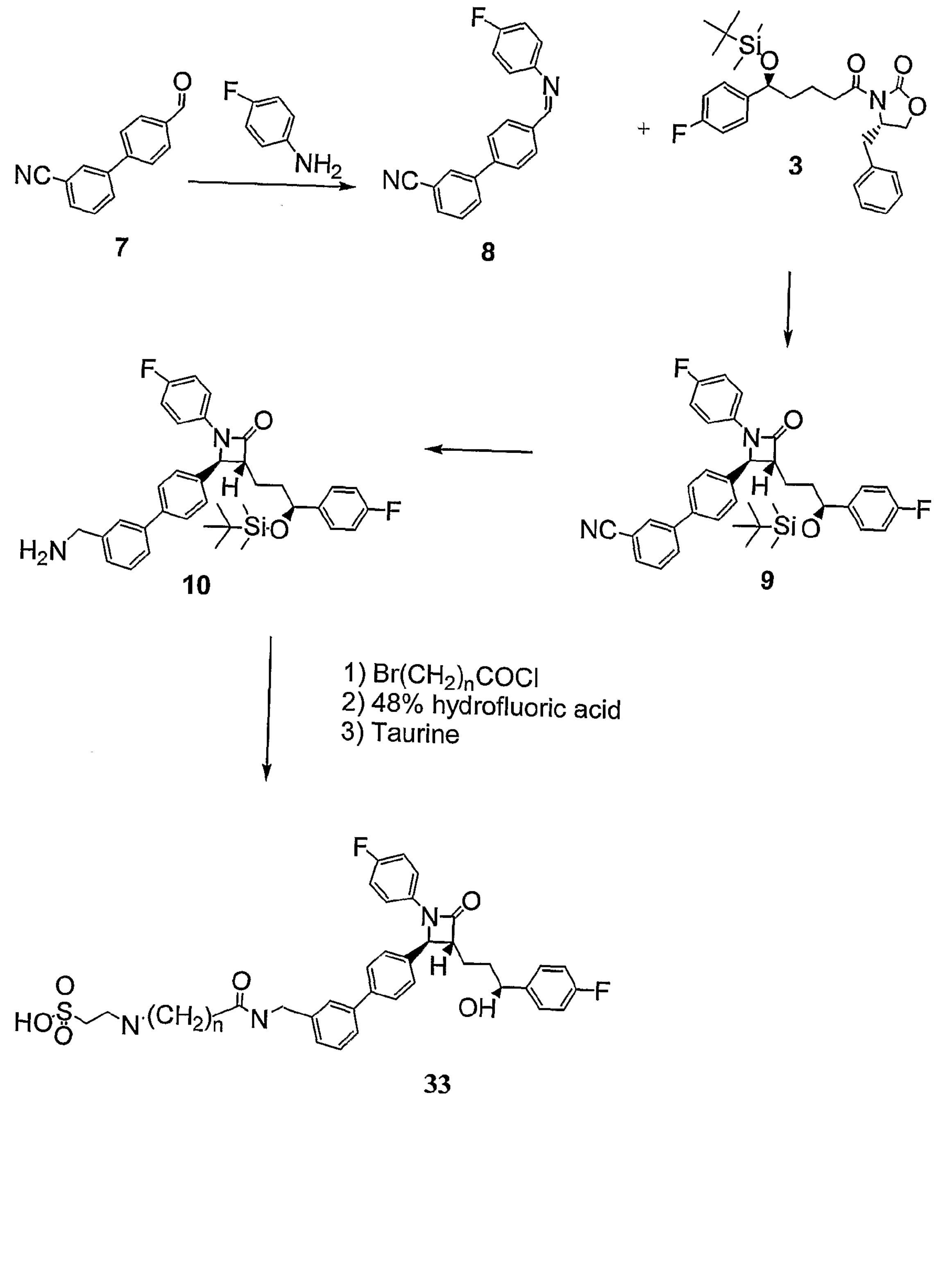
[00289] Example 32. Illustrated in Scheme I below is the general method for the preparation of cholesterol absorption inhibitors of general formula 32. Imines 2 are made by refluxing 4-cyanoaniline with the appropriate aldehyde in isopropanol. Condensation of imine 2 with the benzyloxazolidinone compound 3 using titanium tetrachloride, and subsequent cyclization using N,O-bistrimethylacetamide and catalytic tetra-n-butylammonium fluoride, affords the azetidinone 4. Reduction of the cyano group in 4 to the amine 5 is accomplished under hydrogen atmosphere over excess Raney-Nickel in ethanol and ammonium hydroxide. Acylation with the appropriate acid chloride [Br(CH2)$_n$COCl], followed by reaction with hydrofluoric acid in acetonitrile to remove the silyl protecting groups, and subsequent reaction with taurine provides the finally product 32. It is noted that in this scheme the taurine is for illustration and that a large variety of functional groups can be substituted in its place.

Scheme I



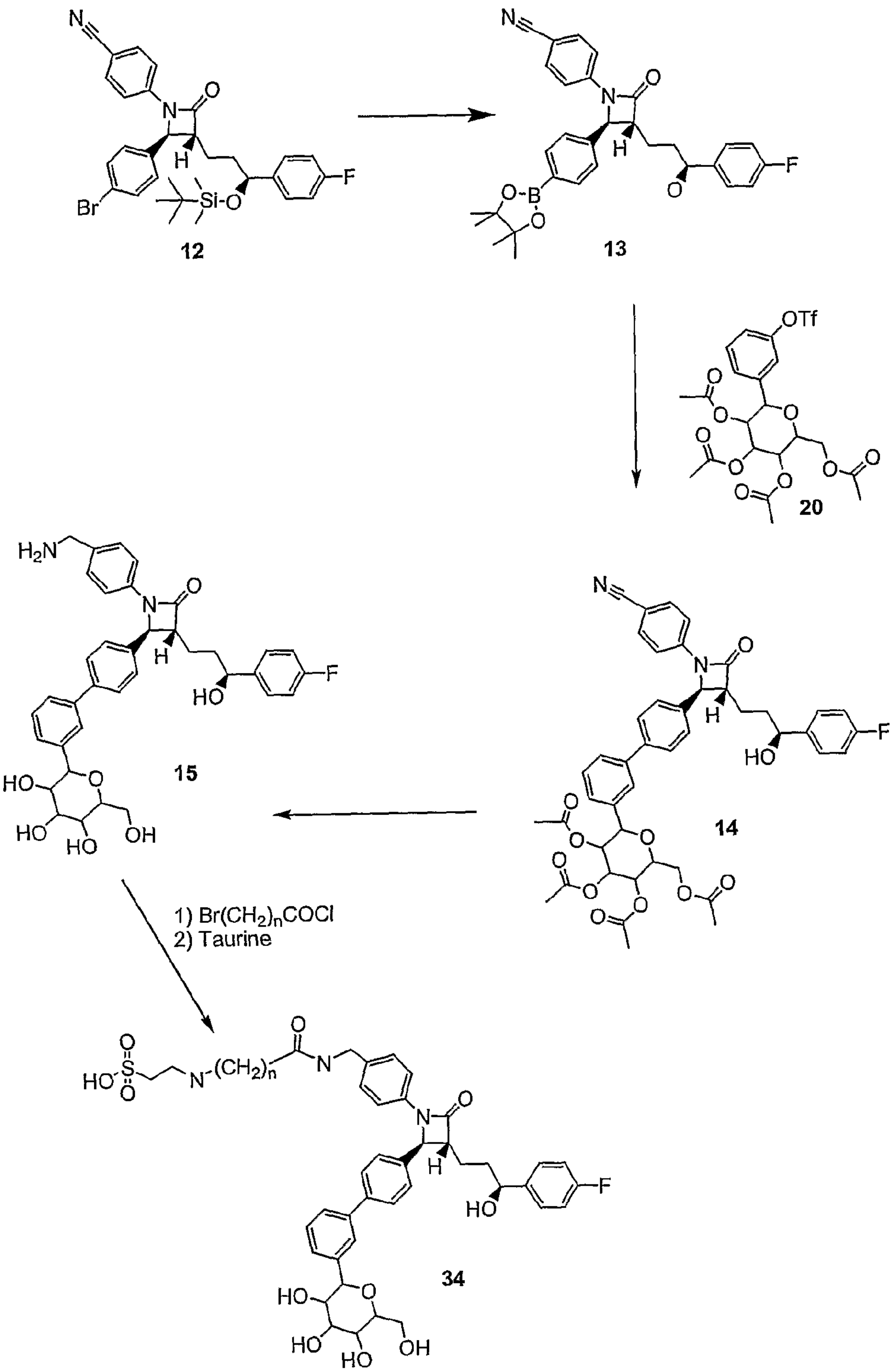
[00290] Example 33. Illustrated in Scheme II below is the general method for the preparation of cholesterol absorption inhibitors of general formula 33. The aldehyde 7 is made by Suzuki coupling of 4-bromobenzaldehyde with 3-cyanophenylboronic acid. Refluxing 4-fluoroaniline with the aldehyde 7 in isopropanol makes the imine 8. Condensation of imine 8 with benzyloxazolidinone compound 3 using titanium tetrachloride and subsequent cyclization, using N,O-bistrimethylacetamide and catalytic tetra-n-butylammonium fluoride, affords the azetidinone 9. Reduction of the cyano group in 9 to the amine 10 is accomplished under hydrogen atmosphere over excess Raney-Nickel in ethanol and ammonium hydroxide. Acylation with the appropriate acid chloride [$Br(CH2)_nCOCl$], followed by reaction with hydrofluoric acid in acetonitrile to remove the silyl protecting groups, and reaction with taurine provides the final product 11. It is noted that in this scheme the taurine is for illustration and that a large variety of functional groups can be substituted in its place.

Scheme II

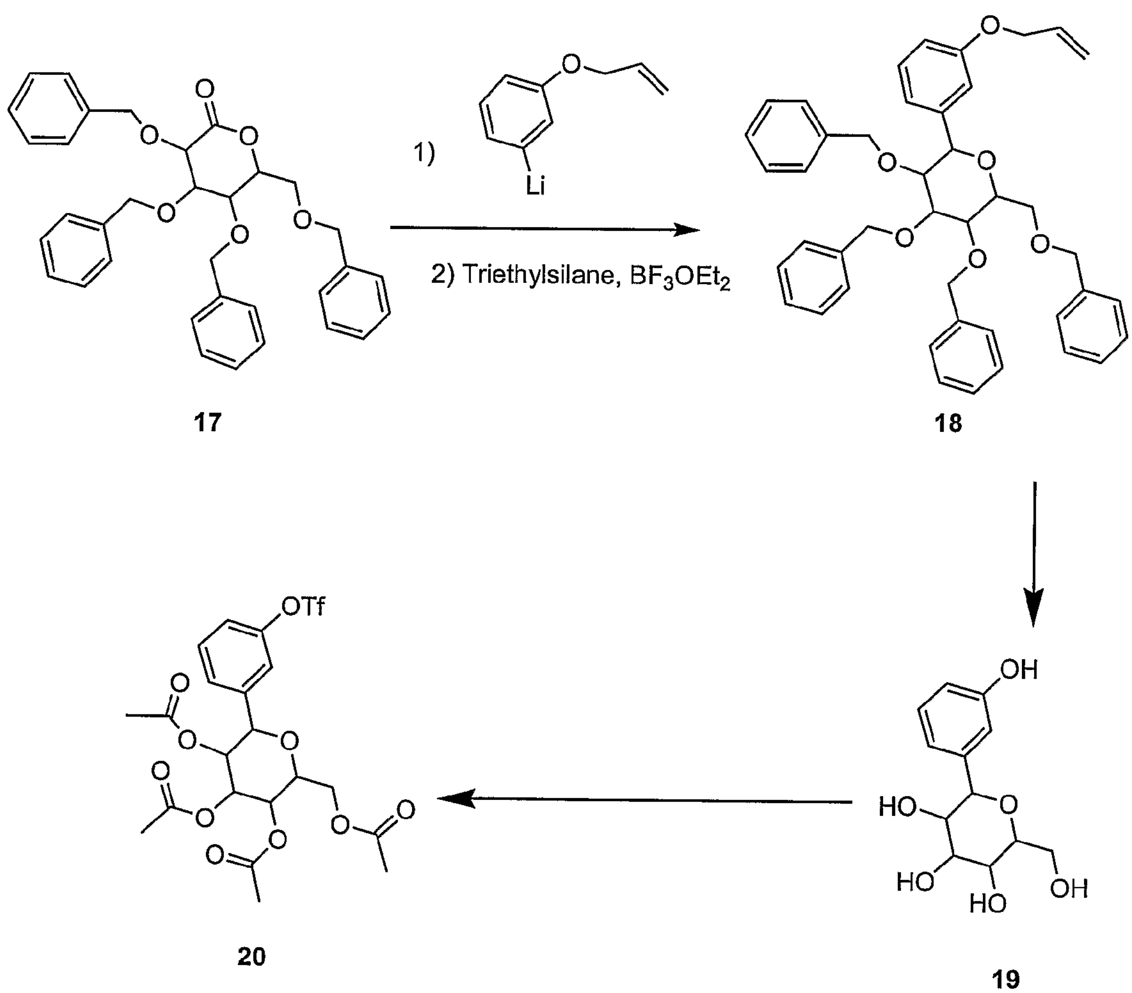

NC
O
F
NH2
N
F
Si
O
O
O
N
O
+
3
7
8
9
10
H
H2N
NC
1) Br(CH2)nCOCl
2) 48% hydrofluoric acid
3) Taurine
HO
S
N
(CH2)n
OH
33

[00291] Example 34. Illustrated in Scheme III below is the general method for the preparation of cholesterol absorption inhibitors of general formula 34. An imine is made by condensing 4-bromobenzaldehyde with 4-cyanoaniline, followed by condensation with the benzyloxazolidinone compound 3 using titanium tetrachloride, and subsequent cyclization, using N,O-bistrimethylacetamide and catalytic tetra-n-butylammonium fluoride, to afford the azetidinone 12. Hydrofluoric acid in acetonitrile is used to remove the silyl protecting group, and coupling to bis(pinacolato)diboron using catalytic palladium affords compound 13. Suzuki coupling with intermediate 20 affords compound 14. Reduction of the cyano group is accomplished under hydrogen atmosphere over excess Raney-Nickel in ethanol and ammonium hydroxide, and acetate groups are removed with triethylamine-methanol-water to provide 15. Acylation with the appropriate acid chloride [$Br(CH2)_nCOCl$] followed by reaction with taurine provides the final product 16. It is noted that in this scheme the taurine is for illustration and that a large variety of functional groups can be substituted in its place.

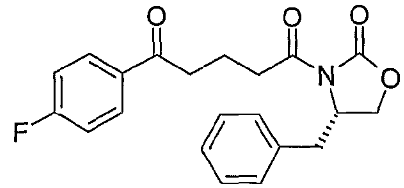
Scheme III



[00292] Synthesis of Intermediate 20: 3-Allyloxyphenyl lithium is reacted with glucopyranolactone 17, followed by reductive cleavage of the hemiketal with triethylsilane and boron trifluoride diethyl etherate to provide benzyl-protected glycoside 18. Removal of the allyl group with palladium catalyst and tri-n-butyltin hydride followed by hydrogenation using palladium on carbon under a hydrogen atmosphere provides phenyl glycoside 19. Reaction with N-phenyltrifluoromethanesulfonimide provides the triflate and peracetylation using acetic anhyride in pyridine afford intermediate 20.

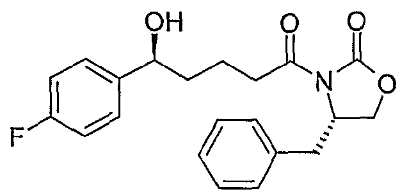


[00293] Example 35. (4S)-4-Benzyl-3-[5-(4-fluorophenyl)-5-oxopentanoyl]-1,3-oxazolidin-2-one



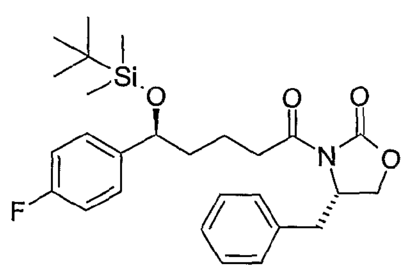
5-(4-Fluorophenyl)-5-oxopentanoic acid (10.08 g, 47.9 mmol) and triethylamine (6.8 mL, 4.94 g, 48.8 mmol) were dissolved in tetrahydrofuran (50 mL). The reaction was cooled to –5 °C (ice/brine bath), trimethylacetyl chloride (6.0 mL, 5.87 g, 48.7 mmol) was added quickly drop-wise and the mixture was warmed to room temperature and stirred for 1.5 h. The reaction was cooled to –5 °C (ice/brine bath) again for 30 min, filtered through Celite®, washed with cold 1:1 hexane-tetrahydrofuran (60 mL) and hexane (120 mL). The filtrate was concentrated, dissolved in N,N-dimethylformamide (16 mL) and to this mixture was added (S)-benzyl-2-oxazolidinone (8.47 g, 47.8 mmol) and 4-dimethylaminopyridine (8.57 g, 70.2 mmol) as solids. The reaction was stirred at room temperature for 20 h, poured into 1.0 N hydrochloric acid (400 mL) and extracted with ethyl acetate (2 x 300 mL). The organic layer was washed with water (400 mL), quarter saturated sodium bicarbonate solution (400 mL), brine (200 mL), dried over sodium sulfate, filtered, and concentrated. The residue was purified by crystallization from hot isopropyl alcohol (75 mL) with slow cooling to room temperature over 16 h. The crystals were filtered cold and washed with cold isopropyl alcohol (50 mL) to afford (4S)-4-benzyl-3-[5-(4-fluorophenyl)-5-oxopentanoyl]-1,3-oxazolidin-2-one (13.87 g, 78% yield) as a white crystalline solid; mp 114.5 °C; R_f 0.29 (1:2 ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03-7.98 (m, 2H), 7.37-7.19 (m, 5H), 7.14 (t, J = 8.7 Hz, 2H), 4.72-4.64 (m, 1H), 4.25-4.15 (m, 2H), 3.32 (dd, J = 13.3, 3.4 Hz, 1H), 3.12-3.01 (m, 4H), 2.78 (dd, J = 13.3, 9.6 Hz, 1H), 2.15 (quint., J = 7.2 Hz, 2H) ppm

[00294] Example 36. (4S)-4-Benzyl-3-[(5S)-5-(4-fluorophenyl)-5-hydroxypentanoyl]-1,3-oxazolidin-2-one



(4S)-4-Benzyl-3-[5-(4-fluorophenyl)-5-oxopentanoyl]-1,3-oxazolidin-2-one (13.87 g, 37.54 mmol) was dissolved in dichloromethane (40 mL). Into a separate flask were added borane-methyl sulfide complex (3.6 mL, ~38 mmol), 1.0 M ®-1-methyl-3,3-diphenyltetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaborole in toluene (1.9 mL, 1.9 mmol) and dichloromethane (20 mL). This mixture was cooled to –5 °C (ice/methanol bath) and the ketone solution was added drop-wise via cannula over 5 min. The reaction was stirred at –5 °C for 5.5 h and then quenched by slow addition of methanol (9 mL), 5% hydrogen peroxide solution (30 mL) and 1 M aqueous sulfuric acid (20 mL) respectively. The reaction was poured into water (500 mL) and extracted with ethyl acetate (500 mL). The organic layer was washed with water (500 mL), 0.1 N hydrochloric acid (300 mL) and brine (300 mL), dried over sodium sulfate, filtered, and concentrated to afford (4S)-4-benzyl-3-[(5S)-5-(4-fluorophenyl)-5-hydroxypentanoyl]-1,3-oxazolidin-2-one, which was used in subsequent reactions without further purification; R_f 0.14 (1:2 ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.24 (m, 5H), 7.19 (d, J = 7.3 Hz, 2H), 7.02 (t, J = 8.9 Hz, 2H), 4.72-4.61 (m, 2H), 4.21-4.13 (m, 2H), 3.27 (dd, J = 13.2, 3.0 Hz, 1H), 2.99-2.94 (m, 2H), 2.74 (dd, J = 13.2, 9.6 Hz, 1H), 2.27 (br s, 1H), 1.88-1.66 (m, 4H) ppm; MS $[M\text{-}OH]^+$ 354.0

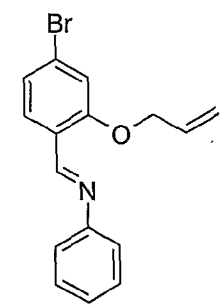
[00295] Example 37. (4S)-4-Benzyl-3-[(5S)-5-{[tert-butyl(dimethyl)silyl]oxy}-5-(4-fluorophenyl)pentanoyl]-1,3-oxazolidin-2-one



(4S)-4-Benzyl-3-[(5S)-5-(4-fluorophenyl)-5-hydroxypentanoyl]-1,3-oxazolidin-2-one (37.54 mmol) was dissolved in N,N-dimethylformamide (40 mL) and then imidazole

(2.97 g, 43.6 mmol) and tert-butyldimethylsilyl chloride (6.12 g, 40.6 mmol) were added. The reaction was stirred at room temperature for 19 h, poured into 0.1 N hydrochloric acid (500 mL) and extracted with 1:1 ethyl acetate-hexane (500 mL). The organic layer was washed with water (2 x 500 mL), brine (300 mL), dried over sodium sulfate, filtered, and concentrated. The residue was purified by crystallization from methanol (55 mL) by heating to a light boil and cooling slowly to room temperature over 18 h. The crystals were filtered cold and washed with cold methanol (45 mL) to afford (4S)-4-benzyl-3-[(5S)-5-{[tert-butyl(dimethyl)silyl]oxy}-5-(4-fluorophenyl)pentanoyl]-1,3-oxazolidin-2-one (16.04 g, 88% yield) as a white crystalline solid; mp 87.6 °C; R_f 0.66 (1:2 ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.18 (m, 7H), 6.99 (t, J = 8.7 Hz, 2H), 4.69-4.61 (m, 2H), 4.18-4.13 (m, 2H), 3.27 (dd, J = 13.5, 3.2 Hz, 1H), 2.96-2.89 (m, 2H), 2.73 (dd, J = 13.5, 9.7 Hz, 1H), 1.82-1.63 (m, 4H), 0.88 (s, 9H), 0.04 (s, 3H), -0.15 (s, 3H) ppm; MS [M-$OSi(CH_3)_2C(CH_3)_3]^+$ 354.0

[00296] Example 38. N-{(1E)-[2-(Allyloxy)-4-bromophenyl]methylene}aniline

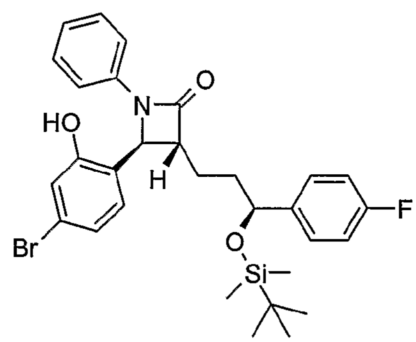


4-Bromosalicylaldehyde (4.02 g, 20.0 mmol) [prepared from 3-bromophenol analogous to the procedure of Casiraghi, et. al. Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1978), 318-21] was dissolved in anhydrous N,N-dimethylformamide (13 mL). Potassium carbonate (3.9 g, 28.0 mmol) was added as a solid to give a yellow suspension. Allyl bromide (2.6 mL, 3.63 g, 30.0 mmol) was added via syringe. The reaction stirred for 17 h at room temperature and was then diluted with water and extracted three times with 1:1 ethyl acetate-hexane. The combined organic layers were washed with water (5x), brine, dried over sodium sulfate, filtered and concentrated to afford 2-(allyloxy)-4-bromobenzaldehyde (4.83 g, 100% yield) as a yellow solid which was used without

further purification in the next step; R_f 0.38 (1:9 ethyl acetate-hexane); MS $[M+H]^+$ 241.0

[00297] 2-(Allyloxy)-4-bromobenzaldehyde (5.05 g, 20.9 mmol) was dissolved with warming in isopropanol (18 mL). Freshly distilled aniline (1.99 g, 21.3 mmol) was added with isopropanol (4 mL) and the reaction was heated to 50 °C. A yellow precipitate formed within 30 min and isopropanol (5 mL) was added to aid stirring. The reaction was stirred at 50 °C for 16 h, by which time proton NMR showed no aldehyde present. The reaction was cooled with stirring. The mixture was diluted with hexane (20 mL), the solid was filtered and washed with the mother liquor, washed with hexane and air dried to afford N-{(1E)-[2-(allyloxy)-4-bromophenyl]methylene}aniline (5.69 g, 86% yield) as a light yellow powder; ^1H NMR (300 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.43-7.36 (m, 2H), 7.27-7.17 (m, 4H), 7.099 (d, J = 1.8 Hz, 1H), 6.06 (ddt, J = 17.2, 10.5, 5.3 Hz, 1H), 5.43 (AB q, J = 17.3, 3.0 Hz, 1H), 5.33 (AB q, J = 10.5, 2.8 Hz, 1H), 4.62 (ddd, J = 5.2, 1.5, 1.5 Hz, 2H) ppm

[00298] Example 39. (3R,4S)-4-(4-Bromo-2-hydroxyphenyl)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-1-phenylazetidin-2-one



2-(Allyloxy)-4-bromobenzaldehyde (2.79 g, 8.83 mmol) and (4S)-4-Benzyl-3-[(5S)-5-{[tert-butyl(dimethyl)silyl]oxy}-5-(4-fluorophenyl)pentanoyl]-1,3-oxazolidin-2-one (3.3 g, 6.8 mmol) were combined in a 100-mL 3-neck round bottom flask fitted with a thermometer and nitrogen inlet. Anhydrous dichloromethane (60 mL) was added to give a light yellow solution which was cooled to –30 °C. Diisopropylethylamine (2.3 mL, 1.71 g, 13.2 mmol) was added via syringe. Titanium tetrachloride (0.86 mL, 1.48 g, 7.82 mmol) was added dropwise over 6 min at an internal temperature between –

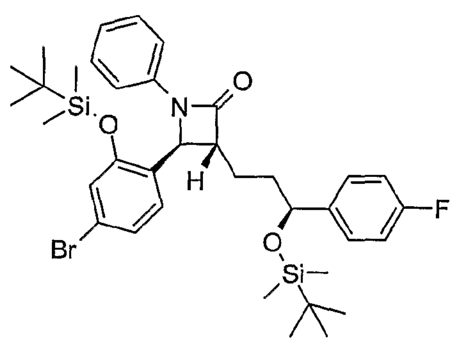
28° to –26 °C to give a reddish brown solution. The reaction stirred under nitrogen for 3 h between –30 to –25 °C and was then cooled to –35 °C and quenched slowly with glacial acetic acid (6 mL) over 6 min. The reaction was poured into a cold (0 °C) 7% tartaric acid solution (125 mL). Ethyl acetate (200mL) was added and the mixture was warmed to room temperature with stirring. A 5% sodium sulfite solution (60mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 200mL). The combined organic layers were washed with a saturated sodium bicarbonate solution, water and brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by chromatography (120 g silica gel, 1% to 90% ethyl acetate-hexane) to afford (4S)-3-[(2R,5S)-2-[(S)-[2-(allyloxy)-4-bromophenyl](anilino)methyl]-5-{[tert-butyl(dimethyl)silyl]oxy}-5-(4-fluorophenyl)pentanoyl]-4-benzyl-1,3-oxazolidin-2-one (4.54 g, 83% yield); R_f 0.38 (1:4 ethyl acetate-hexane); MS $[M+H]^+$ 801.0

[00299] (4S)-3-[(2R,5S)-2-[(S)-[2-(Allyloxy)-4-bromophenyl](anilino)methyl]-5-{[tert-butyl(dimethyl)silyl]oxy}-5-(4-fluorophenyl)pentanoyl]-4-benzyl-1,3-oxazolidin-2-one (1.2 g, 1.5 mmol) was dissolved in anhydrous methyl tert-butyl ether (10 mL) and stirred at room temperature under nitrogen. N,O-bistrimethylsilylacetamide (1.1 mL, 4.5 mmol) was added followed by a catalytic amount (~5 mg) of tetrabutylammonium fluoride trihydrate. The reaction was stirred at room temperature for 19 h, quenched at room temperature with glacial acetic acid (160 μL) and partitioned between ethyl acetate and water and separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with a saturated sodium bicarbonate solution, water, brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by chromatography (120 g silica gel, 1% to 85% ethyl acetate-hexane) to afford (3R,4S)-4-[2-(allyloxy)-4-bromophenyl]-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-1-phenylazetidin-2-one (816 mg, 87% yield); R_f 0.56 (1:4 ethyl acetate-hexane)

[00300] (3R,4S)-4-[2-(Allyloxy)-4-bromophenyl]-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-1-phenylazetidin-2-one (1.34 g, 2.15 mmol) was dissolved in deoxygenated tetrahydrofuran (20 mL). Morpholine (1.8 mL, 1.8 g, 20.6 mmol) was added with additional deoxygenated tetrahydrofuran (5

mL). The reaction was purged with nitrogen and tetrakis(triphenylphosphine)palladium(0) (220 mg, 0.19 mmol) was added. The reaction was purged with nitrogen again. After 1.5 h at room temperature the reaction was diluted with ethyl acetate, washed twice with 1 N hydrochloric acid, saturated sodium bicarbonate solution, water and brine, dried over sodium sulfate and filtered. The solution was treated with activated charcoal, filtered, concentrated and purified by chromatography (40 g silica gel, 6% to 80% ethyl acetate-hexane) to afford (3R,4S)-4-(4-bromo-2-hydroxyphenyl)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-1-phenylazetidin-2-one (1.04 g, 83% yield); R_f 0.38 (1:4 ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.18 (m, 6H), 7.09-6.92 (m, 6H), 5.91 (s, 1H), 4.93 (d, J = 2.3 Hz, 1H), 4.65 (t, J = 5.4 Hz, 1H), 3.06 (ddd, J = 4.8, 2.3, 2.3 Hz, 1H), 1.98-1.77 (m, 4H), 0.86 (s, 9H), 0.006 (s, 3H), -0.16 (s, 3H) ppm; MS $[M-H]^+$ 581.7.

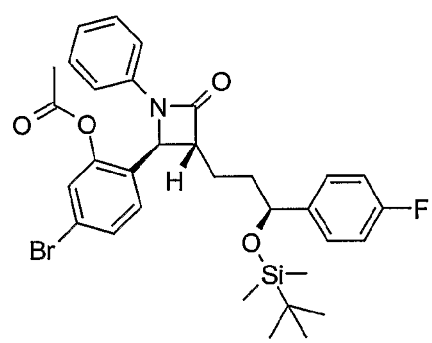
[00301] Example 40. (3R,4S)-4-(4-Bromo-2-{[tert-butyl(dimethyl)silyl]oxy}phenyl)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-1-phenylazetidin-2-one



(3R,4S)-4-(4-Bromo-2-hydroxyphenyl)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy} -3-(4-fluorophenyl)propyl]-1-phenylazetidin-2-one (1.04 g, 1.79 mmol) was dissolved in anhydrous dichloromethane (5 mL), anhydrous N,N-dimethylformamide (5 mL) and stirred under nitrogen at room temperature. 2,6-Lutidine (1.0 mL, 920 mg, 8.6 mmol) was added followed by drop-wise addition of tert-butyldimethylsilyl trifluromethane sulfonate (1.2 mL, 1.38 g, 5.22 mmol). The reaction was stirred under nitrogen at room temperature for 2.25 h. 2,6-Lutidine (0.25 mL, 230 mg, 2.15 mmol) was added followed by addition of tert-butyldimethylsilyl trifluromethane sulfonate

(0.4 mL, 460 mg, 1.74 mmol) and after a total of 4.5 h at room temperature the reaction was diluted with ethyl acetate and water and the layers were separated. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with 0.5 N hydrochloric acid, saturated sodium bicarbonate solution, water (4 times) and brine, dried over sodium sulfate, filtered, concentrated and purified by chromatography (40 g silica gel, 1% to 85% ethyl acetate-hexane) to afford (3R,4S)-4-(4-bromo-2-{[tert-butyl(dimethyl)silyl]oxy}phenyl)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-1-phenylazetidin-2-one (1.23 g, 99% yield); R_f 0.57 (1:4 ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.14 (m, 6H), 7.09-6.91 (m, 6H), 4.99 (d, J = 2.3 Hz, 1H), 4.62 (t, J = 5.6 Hz, 1H), 3.06 (ddd, J = 4.9, 2.5, 2.3 Hz, 1H), 1.97-1.69 (m, 4H), 1.03 (s, 9H), 0.84 (s, 9H), 0.33 (s, 3H), 0.29 (s, 3H), -0.01 (s, 3H), -0.20 (s, 3H) ppm.

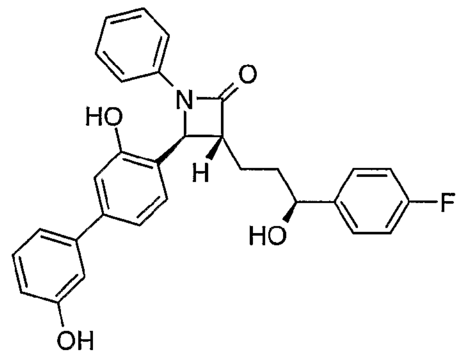
[00302] Example 41. 5-Bromo-2-{(2S,3R)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-oxo-1-phenylazetidin-2-yl}phenyl acetate



(3R,4S)-4-(4-Bromo-2-hydroxyphenyl)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-1-phenylazetidin-2-one (293 mg, 0.50 mmol) was dissolved in anhydrous dichloromethane (3 mL). 4-Dimethylaminopyridine (183 mg, 1.5 mmol) was added followed by acetic anhydride (280 µL, 302 mg, 3.0 mmol). After 1 h the reaction was filtered through a plug of silica gel and eluted with dichloromethane. The solvent was concentrated, azeotroped with toluene and purified by chromatography (40 g silica gel, 1% to 85% ethyl acetate-hexane) to afford 5-bromo-2-{(2S,3R)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-oxo-1-phenylazetidin-2-yl}phenyl acetate (245 mg, 78% yield); R_f 0.47 (1:4 ethyl

acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.16 (m, 9H), 7.14-6.94 (m, 3H), 4.69 (t, J = 5.4 Hz, 1H), 4.64 (d, J = 2.3 Hz, 1H), 3.06 (ddd, J = 4.7, 2.3, 2.2 Hz, 1H), 2.30 (s, 3H), 1.97-1.78 (m, 4H), 0.89 (s, 9H), 0.032 (s, 3H), -0.14 (s, 3H) ppm; MS $[M\text{-}OSi(CH_3)_2C(CH_3)_3]^+$ 493.8

[00303] Example 42. (3R,4S)-4-(3,3'-Dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one

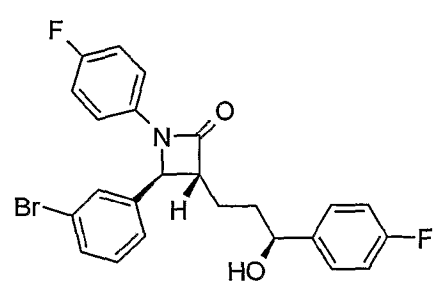


[00304] Using Suzuki coupling methodology, 5-Bromo-2-{(2S,3R)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-oxo-1-phenylazetidin-2-yl}phenyl acetate (100 mg, 0.16 mmol) was combined with 3-hydroxyphenyl boronic acid (29 mg, 0.21 mmol) with deoxygenated toluene (3 mL) and deoxygenated ethanol (1 mL). 2.0 M aqueous potassium carbonate (0.31 mL, 0.31 mmol) was added and the vessel was purged with nitrogen. Tetrakis(triphenylphosphine)palladium(0) (9 mg, 0.008 mmol) was added and the vessel purged again. The reaction was heated to 70 °C for 1.5 h, cooled, diluted with water and extracted with ethyl acetate (2 x). The combined organic layers were washed with water, brine, dried over sodium sulfate, filtered, concentrated and purified by chromatography (40 g silica gel, 20% to 90% ethyl acetate-hexane) to afford 4-{(2S,3R)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl acetate (70 mg, 69% yield)); R_f 0.34 (1:2 ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.17 (m, 10H), 7.06-6.90 (m, 5H), 6.79 (ddd, J = 8.1, 2.5, 0.8 Hz, 1H), 6.03 (br s, 1H), 4.67 (d, J = 2.3 Hz, 1H), 4.64 (t, J = 5.6 Hz, 1H), 3.26 (ddd, J = 4.8, 2.5, 2.4 Hz, 1H), 2.27 (s, 3H), 1.94-1.73 (m, 4H), 0.84 (s, 9H), -0.02 (s, 3H), -0.19 (s, 3H) ppm; MS $[M\text{-}OSi(CH_3)_2C(CH_3)_3]^+$ 508.0

[00305] 4-{(2S,3R)-3-[(3S)-3-{[tert-Butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl acetate (70 mg, 0.11 mmol) was dissolved in methanol (2.45 mL). Water (0.73 mL) was added dropwise followed by triethylamine (2.2 mL) and the reaction stirred at room temperature for 1 h. Toluene (3 mL) and methanol (5 mL) were added and the reaction was concentrated to give 69 mg of crude (3R,4S)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-(3,3'-dihydroxybiphenyl-4-yl)-1-phenylazetidin-2-one which was used without further purification.

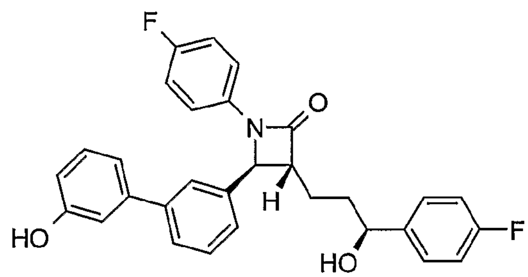
[00306] (3R,4S)-3-[(3S)-3-{[tert-Butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-(3,3'-dihydroxybiphenyl-4-yl)-1-phenylazetidin-2-one (73 mg , 0.122 mmol) was dissolved in acetonitrile (5 mL) and transferred to a polypropylene conical vial. 48% Hydrofluoric acid (1 mL) was added dropwise and the reaction stirred at room temperature for 1 h. The reaction was quenched with 1 N sodium hydroxide (24 mL) and transferred to a flask containing pH 7.4 phosphate buffer (24 mL). The pH of the solution was adjusted to 7.5-8.0 with saturated sodium bicarbonate solution then extracted with ethyl acetate (3x). The combined organic layers were washed with saturated sodium bicarbonate solution (2x), water, brine, dried over sodium sulfate, filtered, concentrated and purified by chromatography (12 g silica gel, 40% to 100% ethyl acetate-hexane) to afford (3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one (53 mg, 69% yield)); ^{1}H NMR (300 MHz, $CDCl_3$)δ 7.30-7.13 (m, 7H), 7.08-6.85 (m, 8H), 6.78 (ddd, J = 8.1, 2.3, 0.9 Hz, 1H), 5.04 (d, J = 2.3 Hz, 1H), 4.61 (t, J = 5.9 Hz, 1H), 3.07 (ddd, J = 5.7, 1.8, 1.5 Hz, 1H), 2.08-1.80 (m, 4H) ppm; MS $[M+H]^+$ 584.0 $[M-H]^-$ 582.0

[00307] Example 43. (3R,4S)-4-(3-bromophenyl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one



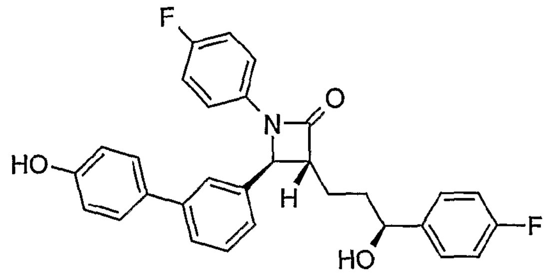
[00308] Synthesized using a similar procedure as Example 39 starting from 4-fluoroaniline and 3-bromobenzaldehyde. The benzylic TBDMS protecting group was removed using 48% hydrofluoric acid as described in Example 42. Purified by chromatography (silica gel, 10% to 60% ethyl acetate-hexane) to afford (3R,4S)-4-(3-bromophenyl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one (86 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.45 (m, 2H), 7.33-7.18 (m, 6H), 7.07-6.91 (m, 4H), 4.72 (t, J = 5.8 Hz, 1H), 4.57 (d, J = 2.4 Hz, 1H), 3.10 (ddd, J = 4.8, 2.4, 2.4 Hz, 1H), 2.12 (br s, 1H), 2.06-1.86 (m, 4H) ppm; MS $[M+HCO_2^-]^-$ 516.0

[00309] Example 44. (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-hydroxybiphenyl-3-yl)azetidin-2-one



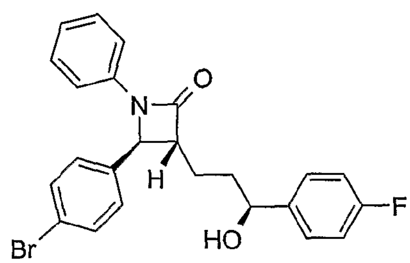
(3R,4S)-4-(3-Bromophenyl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one (43 mg, 0.091 mmol) was coupled with 3-hydroxyphenyl boronic acid (18 mg, 0.13 mmol) under standard Suzuki conditions illustrated by Example 42. Purified by chromatography (silica gel, 10% to 90% ethyl acetate-hexane) to afford (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-hydroxybiphenyl-3-yl)azetidin-2-one (19.7 mg, 45% yield); R_f 0.30 (1:1 ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.40 (m, 3H), 7.34-7.22 (m, 6H), 7.10 (ddd, 7.7, 1.6, 0.9 Hz 1H), 7.04-6.90 (m, 5H), 6.84 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 5.10 (br s, 1H), 4.72 (t, J = 5.9 Hz, 1H), 4.67 (d, J = 2.4 Hz, 1H), 3.16 (ddd, J = 5.0, 2.6, 2.4 Hz, 1H), 2.26 (br s, 1H), 2.08-1.88 (m, 4H) ppm

[00310] Example 45. (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4'-hydroxybiphenyl-3-yl)azetidin-2-one



(3R,4S)-4-(3-Bromophenyl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one (42 mg, 0.089 mmol) was coupled with 4-hydroxyphenyl boronic acid (18 mg, 0.13 mmol) under standard Suzuki conditions illustrated by Example 42. Purified by chromatography (silica gel, 10% to 90% ethyl acetate-hexane) to afford (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4'-hydroxybiphenyl-3-yl)azetidin-2-one (27 mg, 63% yield); R_f 0.31 (1:1 ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.37 (m, 6H), 7.32-7.22 (m, 4H), 7.04-6.87 (m, 6H), 5.24 (br s, 1H), 4.72 (t, J = 6.0 Hz, 1H), 4.67 (d, J = 2.4 Hz, 1H), 3.17 (ddd, J = 5.3, 2.5, 2.4 Hz, 1H), 2.26 (br s, 1H), 2.09-1.88 (m, 4H) ppm

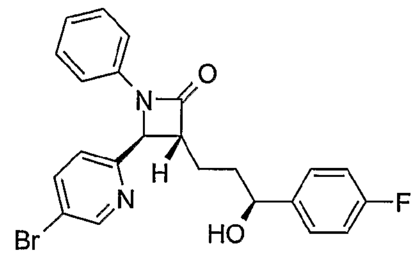
[00311] Example 46. (3R,4S)-4-(4-Bromophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one



[00312] Synthesized using a similar procedure as Example 39 starting from aniline and 4-bromobenzaldehyde. The benzylic TBDMS protecting group was removed using 48% hydrofluoric acid as described in Example 42. Purification by chromatography (40 g silica gel, 10% to 90% ethyl acetate-hexane) afforded (3R,4S)-4-(4-bromophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one (982.6 mg, 75% overall yield) as a clear film; R_f 0.45 (2:3 ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, J = 8.3 Hz, 2H), 7.31-7.19 (m, 8H), 7.07-6.98

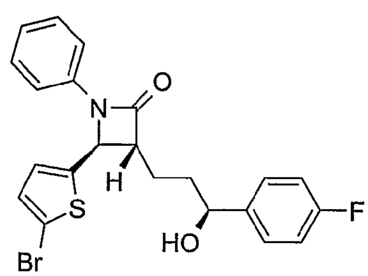
(m, 3H), 4.70 (t, J = 6.1 Hz, 1H), 4.61 (d, J = 2.5 Hz, 1H), 3.04 (dt, J = 7.4, 2.3 Hz, 1H), 2.24 (br s, 1H), 2.03-1.86 (m, 4H) ppm

[00313] Example 47. (3R,4S)-4-(5-Bromopyridin-2-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one



[00314] Synthesized using the same procedure as Example 39 starting from aniline and 5-bromo-2-pyridinecarboxaldehyde (prepared using a procedure described by Wang et. al., Tetrahedron Letters 41 (2000), 4335-4338). The benzylic TBDMS protecting group was removed using 48% hydrofluoric acid as described in Example 42. Purification by chromatography (12 g silica gel, 15% to 90% ethyl acetate-hexane) afforded (3R,4S)-4-(5-bromopyridin-2-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one (23.3 mg, 3% overall yield) as a clear film; R_f 0.07 (1:4 ethyl acetate-hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, J = 2.3 Hz, 1H), 7.80 (dd, J = 8.3, 2.3 Hz, 1H), 7.34-7.29 (m, 3H), 7.24-7.17 (m, 4H), 7.09-6.99 (m, 3H), 4.82 (d, J = 2.5 Hz, 1H), 4.75-4.71 (m, 1H), 3.21 (dt, J = 7.0, 2.3 Hz, 1H), 2.31-1.89 (m, 5H) ppm

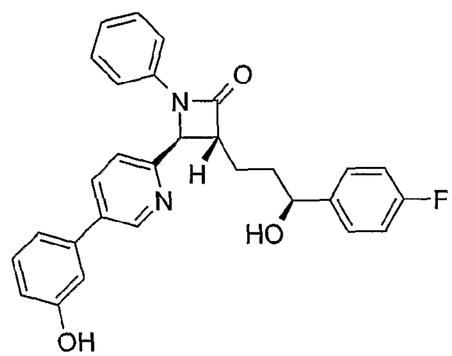
[00315] Example 48. (3R,4S)-4-(5-Bromo-2-thienyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one



[00316] Synthesized using the same procedure as Example 39 starting from aniline and 5-bromo-2-thiophenecarboxaldehyde. The benzylic TBDMS protecting group

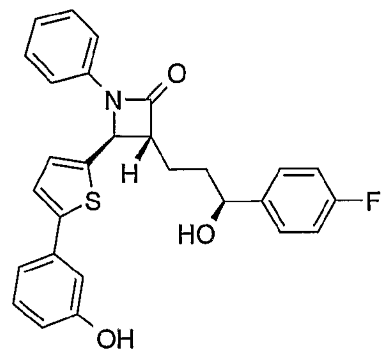
was removed using 48% hydrofluoric acid as described in Example 42. Purification by chromatography (40 g silica gel, 15% to 90% ethyl acetate-hexane) afforded (3R,4S)-4-(5-bromo-2-thienyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one (212.4 mg, 23% overall yield) as a white solid; R_f 0.13 (1:4 ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.21 (m, 6H), 7.10-7.06 (m, 1H), 7.02 (t, J = 8.7 Hz, 2H), 6.89 (dd, J = 19.7, 3.8 Hz, 2H), 4.83 (d, J = 2.4 Hz, 1H), 4.71 (t, J = 5.7 Hz, 1H), 3.25-3.19 (m, 1H), 2.20 (br s, 1H), 2.01-1.83 (m, 4H) ppm

[00317] Example 49. (3R,4S)-3-[(3S)-3-(4-Fluorophenyl)-3-hydroxypropyl]-4-[5-(3-hydroxyphenyl)pyridin-2-yl]-1-phenylazetidin-2-one



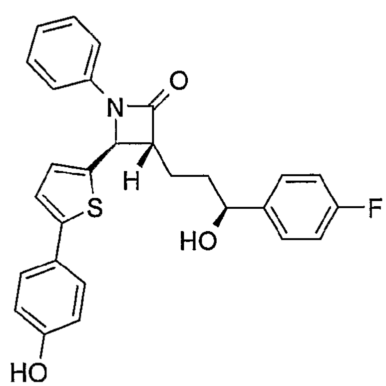
[00318] (3R,4S)-4-(5-Bromopyridin-2-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one (23 mg, 0.051 mmol) was coupled with 3-hydroxyphenyl boronic acid (9.2 mg, 0.067mmol) under standard Suzuki conditions illustrated by Example 42. Purification by chromatography (4 g silica gel, 15% to 100% ethyl acetate-hexane) afforded (3R,4S)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[5-(3-hydroxyphenyl)pyridin-2-yl]-1-phenylazetidin-2-one (20.7 mg, 87% yield) as a clear film; R_f 0.14 (1:1 ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (d, J = 2.2 Hz, 1H), 7.88 (dd, J = 8.2, 2.3 Hz, 1H), 7.86-7.80 (m, 1H), 7.39-7.22 (m, 7H), 7.12-7.02 (m, 3H), 6.96 (t, J = 8.7 Hz, 2H), 6.96-6.91 (m, 1H), 4.97 (d, J = 2.3 Hz, 1H), 4.76-4.72 (m, 1H), 3.28-3.22 (m, 1H), 3.20 (br s, 1H), 2.17-1.90 (m, 4H), 1.80 (br s, 1H) ppm; MS $[M+H]^+$ 469.0

[00319] Example 50. (3R,4S)-3-[(3S)-3-(4-Fluorophenyl)-3-hydroxypropyl]-4-[5-(3-hydroxyphenyl)-2-thienyl]-1-phenylazetidin-2-one



(3R,4S)-4-(5-Bromo-2-thienyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one (90.2 mg, 0.196 mmol) was coupled with 3-hydroxyphenyl boronic acid (32.2 mg, 0.233 mmol) under standard Suzuki conditions illustrated by Example 42. Purification by chromatography (12 g silica gel, 15% to 100% ethyl acetate-hexane) afforded (3R,4S)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[5-(3-hydroxyphenyl)-2-thienyl]-1-phenylazetidin-2-one (77.6 mg, 84% yield) as a clear foam; R_f 0.36 (1:1 ethyl acetate-hexane); ^{1}H NMR (300 MHz, CD_3OD) δ 7.31-6.93 (m, 14H), 6.70 (ddd, J = 8.0, 2.3, 1.0 Hz, 1H), 4.89-4.88 (m, 1H), 4.64-4.59 (m ,1H), 3.77 (br s, 2H), 3.25-3.21 (m, 1H), 1.97-1.83 (m, 4H) ppm; MS $[M-OH]^+$ 456.0

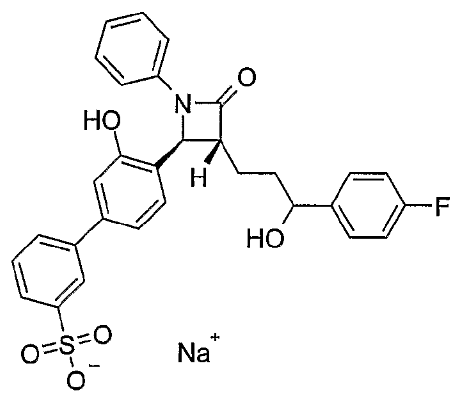
[00320] Example 51. (3R,4S)-3-[(3S)-3-(4-Fluorophenyl)-3-hydroxypropyl]-4-[5-(4-hydroxyphenyl)-2-thienyl]-1-phenylazetidin-2-one



(3R,4S)-4-(5-Bromo-2-thienyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one (69.8 mg, 0.152 mmol) was coupled with 4-hydroxyphenyl boronic acid (25.2 mg, 0.183 mmol) under standard Suzuki conditions illustrated by Example 42. Purification by chromatography (12 g silica gel, 15% to 100% ethyl acetate-hexane) afforded (3R,4S)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[5-(4-hydroxyphenyl)-2-thienyl]-1-phenylazetidin-2-one (40.7 mg, 56% yield) as a clear

foam; R_f 0.39 (1:1 ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64-7.60 (m, 4H), 7.56-7.48 (m, 5H), 7.33-7.27 (m, 2H), 7.25-7.20 (m, 2H), 7.07 (d, J = 8.6 Hz, 2H), 6.81 (br s, 1H), 5.14 (d, J = 2.3 Hz, 1H), 5.00-4.95 (m, 1H), 3.57-3.50 (m, 1H), 2.29-2.11 (m, 4H) ppm; MS $[M+H]^+$ 474.0

[00321] Example 53. Sodium 4'-{(2S,3R)-3-[(3S/R)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-sulfonate



5-Bromo-2-{(2S,3R)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-oxo-1-phenylazetidin-2-yl}phenyl acetate (140.0 mg, 0.223 mmol) was dissolved in acetonitrile (8.0 mL) and 48% hydrofluoric acid (0.8 mL) into a polypropylene Falcon® tube. The reaction was stirred for 4 h at room temperature and then poured into 0.5 M potassium phosphate (50 mL), extracted with 1:1 ethyl acetate-hexane (50 mL), washed with saturated sodium bicarbonate solution (50 mL) and brine (50 mL), dried over sodium sulfate, filtered, concentrated and purified by chromatography (12 g silica gel, 15% to 90% ethyl acetate-hexane) to afford 5-bromo-2-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}phenyl acetate (114.5 mg, 100% yield) as a clear foam; R_f 0.11 (1:4 ethyl acetate-hexane).

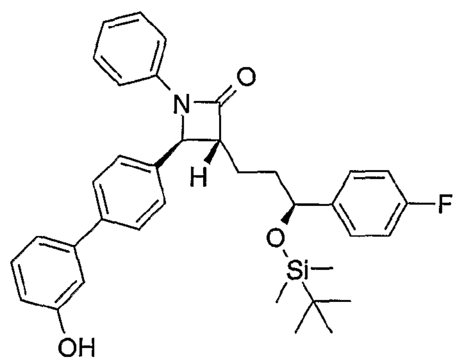
[00322] 5-Bromo-2-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}phenyl acetate (114.5 mg, 0.223 mmol) and 3-thioanisoleboronic acid (48.3 mg, 0.287 mol) were dissolved in toluene (3.0 mL) and ethanol (1.5 mL). A solution of 2.0 M aqueous sodium carbonate (0.215 mL, 0.43 mmol) and solid tetrakis(triphenylphosphine)palladium(0) (14.4 mg, 0.0125 mmol) were added and the vessel was vacuum/nitrogen purged (3x). The reaction was stirred

vigorously for 4 h at 60 °C under a nitrogen atmosphere and then poured into 0.2 N hydrochloric acid (50 mL), extracted with 1:1 ethyl acetate-hexane (75 mL), washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated to afford a mixture of products which was used directly in the next step; R_f 0.79 (2:1 ethyl acetate-hexane) for (3R,4S)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[3-hydroxy-3'-(methylthio)biphenyl-4-yl]-1-phenylazetidin-2-one and 0.84 (2:1 ethyl acetate-hexane) for 4-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-(methylthio)biphenyl-3-yl acetate.

[00323] A 1:1 mixture of (3R,4S)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[3-hydroxy-3'-(methylthio)biphenyl-4-yl]-1-phenylazetidin-2-one and 4-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-(methylthio)biphenyl-3-yl acetate (0.223 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0 °C. 3- Chloroperoxybenzoic acid (64.3 mg, 0.373 mmol) was added in portions while monitoring by LCMS to make the arylsulfoxide. Once addition was complete the reaction was poured into quarter saturated sodium bicarbonate solution (50 mL), extracted with 1:1 ethyl acetate-hexane (75 mL), washed brine (50 mL), dried over sodium sulfate, filtered and concentrated. The residue was dissolved in dichloromethane (10 mL) and the Pummerer rearrangement was effected by the addition of trifluoroacetic anhydride (100 μL, 148.7 mg, 0.708 mmol). The reaction was stirred at room temperature for 4 h and then 3-chloroperoxybenzoic acid (121.7 mg, 0.705 mmol) was added to convert to the sulfone. The mixture was stirred for 15 min at room temperature, concentrated and dissolved in 3:3:1 methanol-triethylamine-water (7 mL) to hydrolyze the acetate and trifluoroacetate groups. The reaction was stirred for 2 h at room temperature, concentrated and dissolved in dichloromethane (10 mL). 3- Chloroperoxybenzoic acid (49.2 mg, 0.285 mmol) was added to oxidize the compound to the sulfonic acid. The reaction was stirred for 10 min at room temperature, diluted with 1:1 ethyl acetate-hexane (50 mL) and extracted with 1% saturated sodium bicarbonate solution (3 x 50 mL). The aqueous layer was acidified with 1.0 N hydrochloric acid (~10 mL), extracted with ethyl acetate (2 x 75 mL), diluted with triethylamine (1.0 mL), concentrated, purified by reverse-phase HPLC (Polaris C18-A 10μ 250 x 21.2 mm

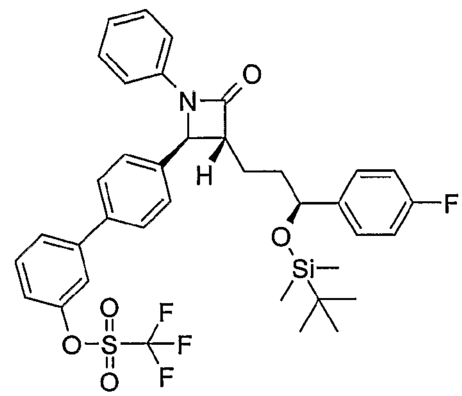
column, 25% to 100% acetonitrile-0.1% trifluoroacetic acid in water) and passed through Dowex® sodium ion exchange resin to afford sodium 4'-{(2S,3R)-3-[(3S/R)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-sulfonate (45.3 mg, 36% yield) as an off-white solid; ^{1}H NMR (300 MHz, CD_3OD) δ 8.04-6.98 (m, 16H), 5.17 (d, J = 2.2 Hz, 0.66H), 5.14 (d, J = 2.2 Hz, 0.33H), 4.70-4.60 (m, 1H), 3.21-3.14 (m, 1H), 2.09-1.89 (m, 4H) ppm; MS $[M-Na]^-$ 546.0

[00324] Example 54. (3R,4S)-3-[(3S)-3-{[tert-Butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-(3'-hydroxybiphenyl-4-yl)-1-phenylazetidin-2-one



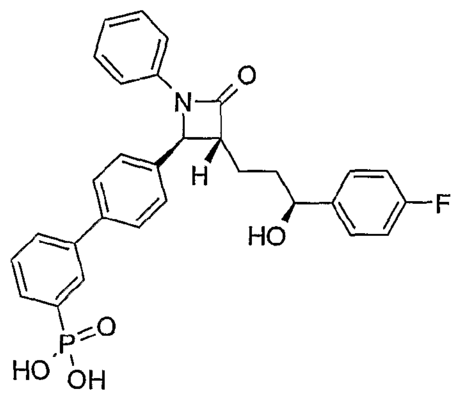
(3R,4S)-4-(3'-{[tert-Butyl(dimethyl)silyl]oxy}biphenyl-4-yl)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-1-phenylazetidin-2-one (0.60 g, 0.86 mmol) was stirred at room temperature in dry methanol (20 mL) under a nitrogen atmosphere. Potassium fluoride (0.10 g, 1.72 mmol) was added and the reaction mixture was stirred 1.5 h at room temperature. The solution was poured into ethyl acetate and washed successively with water (2x), 10% aqueous sodium bicarbonate, water and brine. The organic solution was dried over sodium sulfate, filtered, concentrated and purified by chromatography over silica gel using ethyl acetate-hexane (gradient: 5% ethyl acetate to 50%) to afford (3R,4S)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-(3'-hydroxybiphenyl-4-yl)-1-phenylazetidin-2-one (0.46 g, 92%) as a white foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.57 (d, J = 8.2, Hz, 2H,) 7.37 (d, J = 8.2 Hz, 2H), 6.9-7.4 (m, 12H), 6.8 (m, 1H), 4.9 (br s, 1H), 4.67 (t, J = 6.0 Hz, 1H), 4.63 (d, J = 2.5 Hz, 1H), 3.0-3.1 (m, 1H), 1.8-2.0 (m, 4H), 0.87 (s, 9H), 0.02 (s, 3H), -0.16 (s, 3H)

[00325] Example 55. 4'-{(2S,3R)-3-[(3S)-3-{[tert-Butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl trifluoromethanesulfonate



(3R,4S)-3-[(3S)-3-{[tert-Butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-(3'-hydroxybiphenyl-4-yl)-1-phenylazetidin-2-one (0.46 g, 0.79 mmol) was stirred at room temperature in dry dichloromethane (15 mL) under a nitrogen atmosphere. N-Phenyltrifluoromethanesulfonimide (0.39 g, 1.09 mmol), triethylamine (0.23 mL, 1.65 mmol) and 4-(dimethylamino)pyridine (0.02 g, 0.2 mmol) were added in succession and the reaction mixture was stirred 2 h at room temperature. The solution was poured into 0.5N aqueous hydrochloric acid (20 mL) and extracted with ethyl acetate. The organic phase was washed successively with water, 10% aqueous sodium bicarbonate, water and brine. The organic solution was dried over sodium sulfate, filtered and the solvent was removed in vacuo to afford 4'-{(2S,3R)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl trifluoromethanesulfonate as a white foam (0.56 g, 100%) by chromatography over silica gel using ethyl acetate-hexane (gradient: 5% ethyl acetate to 50%) ^{1}H NMR (300 MHz, $CDCl_3$) δ6.9-7.3 (m, 17H), 4.68 (t, J = 5.7 Hz, 1H), 4.65 (d, J = 2.5 Hz, 1H), 3.0-3.1 (m, 1H), 1.8-2.0 (m, 6H), 0.88 (s, 9H), 0.02 (s, 3H), -0.16 (s, 3H).

[00326] Example 56. (4'-{(2S,3R)-3-[(3S)-3-(4-Fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)phosphonic acid

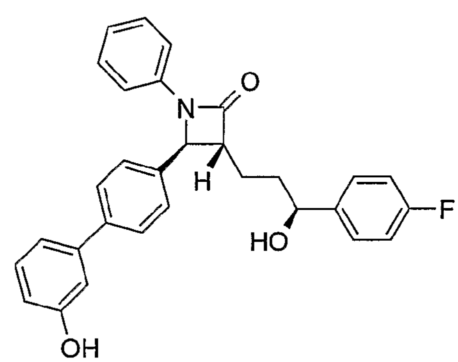


[00327] This reaction was performed using a PersonalChemistry™ microwave instrument set at normal absorbance, fixed hold time and 30 sec pre-stirring. A 10-mL reaction vial was charged with 4'-{(2S,3R)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl trifluoromethanesulfonate (0.27 g, 0.38 mmol), dimethyl phosphite (0.070 mL, 0.76 mmol) and triethylamine (0.15 mL, 1.08 mmol) in toluene (4 mL). Nitrogen was bubbled through the stirred solution for 5 min, tetrakis(triphenylphosphine)palladium(0) (0.1 g) was added, and the solution was covered with a blanket of nitrogen and sealed. The reaction mixture was heated for 11 min at 160 °C, then cooled to room temperature and diluted with ethyl acetate. The yellow solution was washed successively with 0.5 M hydrochloric acid (20 mL) water (3x) and brine. The organic solution was dried over sodium sulfate, filtered and the solvent was removed by rotary evaporation under reduced pressure. Pure dimethyl (4'-{(2S,3R)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)phosphonate was obtained as a white foam (0.26 g, 65%) by chromatography over silica gel using ethyl acetate-hexane (gradient: 5% ethyl acetate to 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ8.00 (dt, J = 14.2, 1.5 Hz, 1H), 7.60 (d, J = 8.5 Hz, 2H), 7.40(d, J = 8.5 Hz, 2H), 6.9-7.8 (m, 12H), 4.68 (t, J = 5.7 Hz, 1H), 4.64 (d, J = 2.4 Hz, 1H), 3.81 (d, J = 0.9 Hz, 1H), 3.77 (d, J = 0.9 Hz, 1H), 3.0-3.1 (m, 1H), 1.8-2.2 (m, 4H), 0.88 (s, 9H), 0.02 (s, 3H), -0.16 (s, 3H) ppm

[00328] A solution of dimethyl (4'-{(2S,3R)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-oxo-1-phenylazetidin-2-

yl}biphenyl-3-yl)phosphonate (0.32 g, 0.47 mmol) in dry dichloromethane (15 mL) under nitrogen was cooled in an ice bath and bromotrimethylsilane (0.30 mL, 2.27 mmol) was dripped in over 5 min. The reaction mixture was stirred at room temperature for 3 h, then poured into ice water (20 mL) and extracted with ethyl acetate. The organic solution was washed successively with water (2x) and brine. The organic solution was dried over sodium sulfate, filtered and the solvent was removed by rotary evaporation under reduced pressure. The residue was purified by reverse-phase HPLC (Polaris C18-A 10μ 250 x 21.2 mm column, 20% to 70% acetonitrile-0.1% trifluoroacetic acid in water) to afford (4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)phosphonic acid (0.25 g, 99%) as a white powder; ^{1}H NMR (300 MHz, CD_3OD) δ8.04 (br d, J = 14.2 Hz, 1H) 7.68 (d, J = 8.5 Hz, 2H), 7.50(d, J = 8.5 Hz, 2H), 7.0-7.8 (m, 12H), 4.93 (d, J = 2.2 Hz, 1H), 4.63 (t, J = 5.2 Hz, 1H), 3.1-3.2 (m, 1H), 1.8-2.1 (m, 4H) ppm; MS $[M-H]^-$ 531, $[2M-H]^-$ 1061

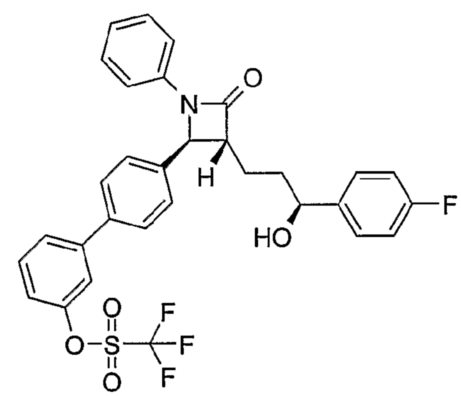
[00329] Example 57. (3R,4S)-3-[(3S)-3-(4-Fluorophenyl)-3-hydroxypropyl]-4-(3'-hydroxybiphenyl-4-yl)-1-phenylazetidin-2-one



(3R,4S)-3-[(3S)-3-(4-Fluorophenyl)-3-hydroxypropyl]-4-(3'-hydroxybiphenyl-4-yl)-1-phenylazetidin-2-one was synthesized in a manner similar to that described in Example 42. (3R,4S)-4-(3'-{[tert-Butyl(dimethyl)silyl]oxy}biphenyl-4-yl)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-1-phenylazetidin-2-one (0.60 g, 0.86 mmol) was stirred at room temperature in acetonitrile (18 mL) in a 40 ml polypropylene vial fitted with a screw cap. Hydrogen fluoride (48% aqueous, 2.0 mL, 48 mmol) was dripped in and stirring was continued at room temperature overnight. The reaction mixture was poured into an aqueous solution of 1 N sodium hydroxide

(45 mL) buffered with 1 M sodium phosphate (45 mL, pH 7.4), then the pH of the solution was brought to pH 8 with the addition of aqueous 10% sodium bicarbonate solution. The mixture was extracted with ethyl acetate and the organic solution was washed successively with 10% sodium bicarbonate solution (2x), water (2x) and brine. The organic solution was dried over sodium sulfate, filtered and the solvent was removed by rotary evaporation under reduced pressure. Pure (3R,4S)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-hydroxybiphenyl-4-yl)-1-phenylazetidin-2-one was obtained as a white foam (0.35 g, 87%) by chromatography over silica gel using ethyl acetate-hexane (gradient: 10% ethyl acetate to 60%) ^{1}H NMR (300 MHz, $CDCl_3$) δ7.56 (d, J = 8.2, Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 7.0-7.3 (m, 12H), 6.80-6.86 (m, 1H), 5.00 (br s, 1H), 4.74 (t, J = 6.2 Hz, 1H), 4.69 (d, J = 2.2 Hz, 1H), 3.1-3.2 (m, 1H), 2.20 (br s, 1H), 1.8-2.1 (m, 4H) ppm; MS $[M+HCO_2^-]^-$ 512

[00330] Example 58. 4'-{(2S,3R)-3-[(3S)-3-(4-Fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl trifluoromethanesulfonate

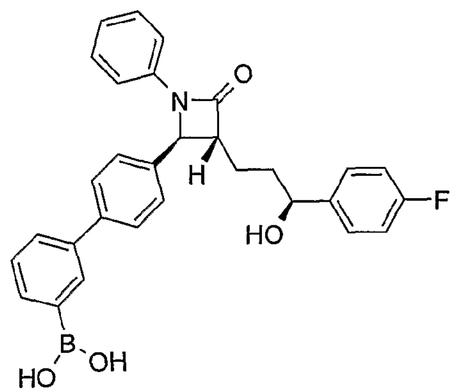


(3R,4S)-3-[(3S)-3-(4-Fluorophenyl)-3-hydroxypropyl]-4-(3'-hydroxybiphenyl-4-yl)-1-phenylazetidin-2-one (0.353 g, 0.77 mmol) was stirred at room temperature in dry dichloromethane (15 mL) under a nitrogen atmosphere.

Phenyltrifluoromethanesulfonimide (0.38 g, 1.69 mmol), triethylamine (0.23 mL, 1.65 mmol) and 4-dimethylaminopyridine (0.02 g, 0.2 mmol) were added in succession and the reaction mixture was stirred 1 h at room temperature. The solution was poured into 0.5 N hydrochloric acid (20 mL) and extracted with ethyl acetate. The organic phase was washed successively with water, 10% aqueous sodium bicarbonate, water and brine. The organic solution was dried over sodium sulfate, filtered and the

solvent was removed by rotary evaporation under reduced pressure. Pure 4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl trifluoromethanesulfonate was obtained as a white foam (0.35 g, 76%) by chromatography over silica gel using ethyl acetate-hexane (gradient: 5% ethyl acetate to 50%); ^{1}H NMR (300 MHz, $CDCl_3$) δ7.0-7.6 (m, 17H), 4.74 (t, J = 6.4 Hz, 1H), 4.72 (d, J = 2.2 Hz, 1H), 3.1-3.2 (m, 1H), 2.16 (br s, 1H), 1.9-2.1 (m, 4H) ppm; MS $[M+HCO_2^-]^-$ 644

[00331] Example 59. (4'-{(2S,3R)-3-[(3S)-3-(4-Fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)boronic acid

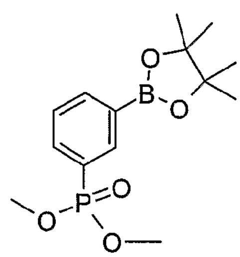


4'-{(2S,3R)-3-[(3S)-3-(4-Fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl trifluoromethanesulfonate (0.15 g, 0.25 mmol), bis(pinacolato)diboron (0.70 g, 0.27 mmol), potassium acetate (0.80 g, 0.81 mmol) and dichloro[1,1'-bis(diphenylphosphino) ferrocene]palladium(II) (0.020 g, 0.03 mmol) were combined in dimethylsulfoxide (7 mL) in a 40-mL screw-cap vial at room temperature. The mixture was covered with a nitrogen atmosphere, the vial was sealed and the reaction was heated overnight at 80 °C. The reaction mixture was cooled to room temperature, poured into water and extracted with ethyl acetate. The organic phase was washed successively with water (2x) and brine, dried over sodium sulfate, filtered and the solvent was removed by rotary evaporation under reduced pressure. Pure (3R,4S)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenyl-4-[3'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)biphenyl-4-yl]azetidin-2-one was obtained as a white foam (0.097 g, 67%) by chromatography over silica gel using ethyl acetate-hexane (gradient: 5% ethyl acetate to 70%) ^{1}H NMR (300 MHz, $CDCl_3$)

δ8.01(br s, 1H), 7.75-7.85 (m, 1H), 7.0-7.7 (m, 15H), 4.74 (t, J = 6.2 Hz, 1H), 4.69 (d, J = 2.2 Hz, 1H), 3.0-3.2 (m, 1H), 1.50 (br s, 1H), 1.8-2.1 (m, 4H), 1.35 (s, 6H), 1.24 (s, 6H) ppm; MS $[M+HCO_2^-]^-$ 577

[00332] (3R,4S)-3-[(3S)-3-(4-Fluorophenyl)-3-hydroxypropyl]-1-phenyl-4-[3'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)biphenyl-4-yl]azetidin-2-one (0.020 g, 0.034 mmol) was dissolved in ethanol (3 mL) and water (1 mL) at room temperature. Solid sodium carbonate (0.10 g, 1.2 mmol) was added and the mixture was rapidly stirred 2 h at room temperature. The solution was poured into 0.5 N hydrochloric acid (4 mL) and extracted with ethyl acetate. The organic phase was washed successively with water (2x) and brine, then dried over sodium sulfate, filtered and the solvent was removed by rotary evaporation under reduced pressure. The residue was purified by reverse-phase HPLC (Polaris C18-A 10μ 250 x 21.2 mm column, 40% to 75% acetonitrile-0.1% trifluoroacetic acid in water) to afford (4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)boronic acid as a white powder (0.012 g, 70%); ^{1}H NMR (300 MHz, CD_3OD) δ7.83 (br s, 1H), 7.0-7.7 (m, 16H), 4.92 (d, J = 2.7 Hz, 1H), 4.63 (t, J = 6.2 Hz, 1H), 3.1-3.2 (m, 1H), 1.8-2.1 (m, 4H) ppm; MS $[M+HCO_2^-]^-$ 540

[00333] Example 60. Dimethyl [3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]phosphonate



3-Chlorophenol (0.50 g, 3.89 mmol) was stirred at room temperature in dry dichloromethane (20 mL) under a nitrogen atmosphere. Phenyltrifluoromethanesulfonimide (1.80 g, 5.0 mmol), triethylamine (0.90 mL, 6.4 mmol) and 4-dimethylaminopyridine (0.10 g, 0.8 mmol) were added in succession and the reaction mixture was stirred 2 h at room temperature. The solution was poured into 0.5 N hydrochloric acid (20 mL) and extracted with ethyl acetate. The organic phase was washed successively with water, 10% aqueous sodium bicarbonate and

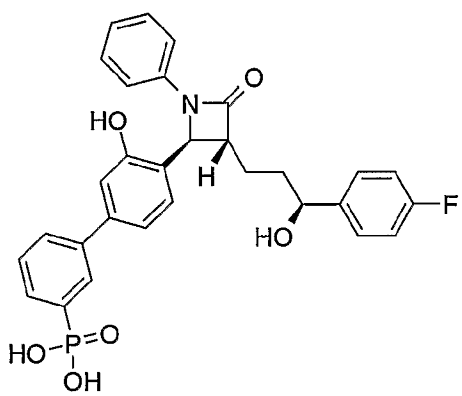
brine. The organic solution was dried over sodium sulfate, filtered and the solvent was removed by rotary evaporation under reduced pressure. Pure 3-chlorophenyl trifluoromethanesulfonate was obtained as a colorless oil (0.92 g, 91%) by chromatography over silica gel using ethyl acetate-hexane (gradient: 5% to 50% ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ7.16-7.50 (m) ppm

[00334] This reaction was performed using a PersonalChemistry™ microwave instrument set at normal absorbance, fixed hold time and 30 sec pre-stirring. A 10-mL reaction vial was charged with 3-chlorophenyl trifluoromethanesulfonate (0.60 g, 2.30 mmol), dimethyl phosphite (0.42 mL, 4.58 mmol) and triethylamine (0.64 mL, 4.59 mmol) in toluene (4 mL). Nitrogen was bubbled through the stirred solution for 5 min, the tetrakis(triphenylphosphine)palladium(0) (0.1 g) was added, the solution was covered with a blanket of nitrogen and sealed. The reaction mixture was heated 11 min at 160 °C, then cooled to room temperature and diluted with ethyl acetate. The yellow solution washed successively with water (3x) and brine. The organic solution was dried over sodium sulfate, filtered and the solvent was removed by rotary evaporation under reduced pressure. Pure dimethyl (3-chlorophenyl)phosphonate was obtained as a colorless oil (0.27 g, 57%) by chromatography over silica gel using ethyl acetate-hexane (gradient: 5% ethyl acetate to 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ7.77 (br d, J = 13.7 Hz, 1H), 7.68 (ddt, J = 13.0,7.5, 1.4 Hz, 1H), 7.53 (dquint., J = 8.0, 1.1 Hz, 1H), 7.38-7.45 (m, 1H), 3.79 (s, 3H), 3.75 (s, 3H) ppm; MS $[M+H]^+$ 221, $[2M+H]^+$ 441

[00335] Bis(dibenzylidineacetone)palladium(0) (0.10 g, 0.17 mmol and tricyclohexylphosphine (0.12 g, 0.43 mmol) were stirred 30 min in dry dioxane (1.0 mL) under an atmosphere of nitrogen at room temperature. Dimethyl (3-chlorophenyl)phosphonate (0.50 g, 2.26 mmol), bis(pinacolato)diboron (0.70 g, 0.27 mmol) and potassium acetate (0.30 g, 0.30 mmol) were mixed in dry dioxane (3.0 mL) at room temperature under a nitrogen atmosphere in a separate flask. A portion of the palladium catalyst solution (0.20 mL) was syringed into the flask containing the chlorophosphonate and this mixture was heated at 80 °C. Additional 0.2 mL portions of the catalyst solution were syringed into the reaction mixture after 4 h and 8 h of heating at 80 °C, then heating was continued overnight at 80 °C. The reaction mixture

was filtered through Celite® and the solvent was removed by rotary evaporation under reduced pressure. Chromatography over silica gel using ethyl acetate-hexane (gradient: 0% ethyl acetate to 80%) dimethyl [3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]phosphonate as a colorless oil (0.41 g). ^{1}H NMR showed a 60:40 mixture of product plus recovered starting material. This mixture was used as is in the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ8.22 (d, J = 13.2 Hz, 1H), 7.95-8.00 (m, 1H), 7.88 (ddt, J = 13.0,7.5, 1.4 Hz, 1H), 7.43-7.50 (m, 1H), 3.76 (s, 3H), 3.73 (s, 3H) ppm; MS $[M+H]^+$ 312, $[2M+H]^+$ 625

[00336] Example 61. (4'-{(2S,3R)-3-[(3S)-3-(4-Fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)phosphonic acid



(3R,4S)-4-(4-Bromo-2-{[tert-butyl(dimethyl)silyl]oxy}phenyl)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-1-phenylazetidin-2-one (0.080 g, 0.11 mmol), crude dimethyl [3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]phosphonate (0.054 g total, 0.030 g calculated, 0.096 mmol) and aqueous 2 M potassium carbonate (0.12 mL, 0.24 mmol) were mixed in ethanol (1.0 mL) and toluene (3.0 mL). The solution was deoxygenated by bubbling nitrogen through the mixture for 5 min while stirring. Tetrakis(triphenylphosphine)palladium(0) (0.05 g) was added and the reaction was heated for 3 h at 70 °C under an atmosphere of nitrogen. The reaction was cooled to room temperature, diluted with ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated by rotary evaporation under reduced pressure. The product was purified by chromatography over silica gel using ethyl acetate-hexane (gradient: 10% ethyl acetate to 80%) to afford dimethyl (3'-{[tert-butyl(dimethyl)silyl]oxy}-4'-{(2S,3R)-3-[(3S)-3-{[tert-

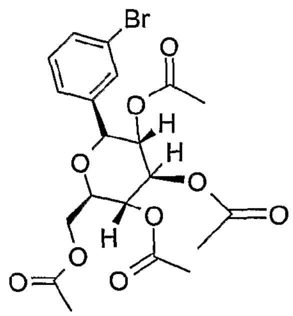
butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)phosphonate as a colorless syrup (0.065 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ6.9-8.0 (m, 16H), 5.09 (d, J = 2.2 Hz, 1H), 4.64 (d, J = 6.1 Hz, 1H), 3.79 (d, J = 2.4 Hz, 3H), 3.76 (d, J = 2.4 Hz, 3H), 3.05-3.15 (m, 1H), 1.8-2.0 (m, 4H), 1.06 (s, 9H), 0.85 (s, 9H), 0.36 (s, 3H), 0.33 (s, 3H), 0.00 (s, 3H), -0.20 (s, 3H) ppm

[00337] Dimethyl (3'-{[tert-butyl(dimethyl)silyl]oxy}-4'-{(2S,3R)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)phosphonate (0.047 g, 0.058 mmol) was stirred at room temperature in dry methanol (2 mL) under a nitrogen atmosphere. Potassium fluoride (0.02 g, 0.34 mmol) was added and the reaction mixture was stirred for 30 min at room temperature. The solution was poured into ethyl acetate and washed successively with water (2x), and brine. The organic solution was dried over sodium sulfate, filtered and the solvent was removed by rotary evaporation under reduced pressure. Dimethyl (4'-{(2S,3R)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)phosphonate was obtained as a colorless glass (0.041 g, 100%) was used directly in the next reaction without further purification; MS $[M-H]^+$ 688

[00338] A solution of dimethyl (4'-{(2S,3R)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)phosphonate (0.041 g, 0.059 mmol) in dry dichloromethane (5 mL) under nitrogen was cooled in ice and bromotrimethylsilane (0.030 mL, 0.30 mmol) was dripped in over 5 min. The reaction mixture was stirred at room temperature for 3 h, then methanol (1 mL) was added and the reaction was partitioned between water and ethyl acetate. The organic solution was washed successively with water (2x) and brine. The organic solution was dried over sodium sulfate, filtered and the solvent was removed by rotary evaporation under reduced pressure. The residue was purified by reverse-phase HPLC (Polaris C18-A 10μ 250 x 21.2 mm column, 30% to 59% acetonitrile-0.1% trifluoroacetic acid in water) to afford (4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)phosphonic acid as a white powder (0.014 g, 44%); ^{1}H NMR (300 MHz, CD_3OD) δ8.0 (d, J = 13.6 Hz, 1H), 6.9-7.8 (m, 15H), 5.17 (d, J = 2.1 Hz,

1H), 4.63 (d, J = 5.2 Hz, 1H), 3.15-3.25 (m, 1H), 1.8-2.1 (m, 4H) ppm; MS $[M-H]^+$ 546, $[2M-H]^+$ 1093.

[00339] Example 62. (1S)-2,3,4,6-Tetra-O-acetyl-1,5-anhydro-1-(3-bromophenyl)-D-glucitol



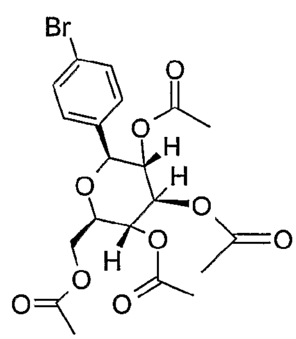
D-Glucopyranose (1.0 g, 5.55 mmol) was dissolved in 5 mL of acetic anhydride and 7 mL of pyridine at 0 °C. To this mixture was added 4-dimethylaminopyridine (200 mg, 1.63 mmol), and the reaction was stirred while warming to room temperature. TLC (40% ethyl acetate-hexane) after 18 h showed complete consumption of the starting material and formation of a higher running spot. The reaction was poured into 50 mL of water and extracted into dichloromethane (3 x 50 mL). The organic layers were combine, washed with 1 N hydrochloric acid (3 x 20 mL), dried over sodium sulfate, filtered, concentrated and purified by column chromatography (50 g silica gel, 40% ethyl acetate-hexane) to afford 1,2,3,4,6-penta-O-acetyl- α-D-glucopyranose (2.10 g, 5.37 mmol).

[00340] 1,2,3,4,6-penta-O-acetyl- α-D-glucopyranose (1.0 g, 2.60 mmol) was dissolved in 20 mL of dichloromethane and 1.90 mL of hydrobromic acid (33% in acetic acid) at 0 °C, and the reaction was stirred while warming to room temperature. TLC (40% ethyl acetate-hexane) after 18 h showed complete consumption of the starting material and formation of a higher running spot. The reaction was slowly diluted with saturated sodium bicarbonate (25 mL), extracted into dichloromethane (2 x 100 mL), dried over sodium sulfate, filtered and concentrated to afford 2,3,4,6-tetra-O-acetyl- α-D-glucopyranosyl bromide which was used without purification.

[00341] Magnesium (0) (400 mg) was suspended in 17 mL of anhydrous diethyl ether, and to the suspension was added 100 μL of 1,2-dibromoethane. 1,3-

dibromobenzene (3.8 g, 16.08 mmol) was added at a rate to keep a moderate reflux. After Grignard formation was complete (magnesium consumed and the reaction cooled), 2,3,4,6-tetra-O-acetyl- α-D-glucopyranosyl bromide (0.34 g, 0.80 mmol in 8mL of anhydrous diethyl ether) was added drop-wise. The reaction was refluxed for 5 h, cooled to room temperature and poured into a separatory funnel with 20 mL of water. The flask was rinsed with 50 mL of diethyl ether and 3 mL of acetic acid (to dissolve the magnesium salts) and added to the seperatory funnel. The layers were separated and the aqueous layer was collected and concentrated in vacuo. The white pasty solid was dissolved in 15 mL of pyridine and 10 mL of acetic anhydride. After 20 h at room temperate the reaction was poured into 150 mL of water and extracted into dichloromethane (3 x 150 mL). The organic layers were combine, washed with 1 N hydrochloric acid (3 x 50 mL), dried over sodium sulfate, filtered, concentrated and purified by column chromatography (12 g silica gel, 5% to 95% ethyl acetate-hexane) to afford (1S)-2,3,4,6-tetra-O-acetyl-1,5-anhydro-1-(3-bromophenyl)-D-glucitol (0.178 g, 0.36 mmol, 45% yield) as a white foam; R_f 0.4 (40% ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (m, 2H) 7.25 (m, 2H), 5.27-5.35 (m, 1H), 5.21 (t, J = 9.6 Hz, 1H), 5.03 (t, J = 9.7 Hz, 1H), 4.36 (d, J = 9.9 Hz, 1H), 4.23-4.32 (m, 1H) 4.08-4.18 (m, 1H) 3.80-3.85 (m, 1H) 2.09 (s, 3H), 2.06 (s, 3H), 1.99 (s, 3H), 1.84 (s, 3H) ppm; MS $[M+H]^+$ 488.4

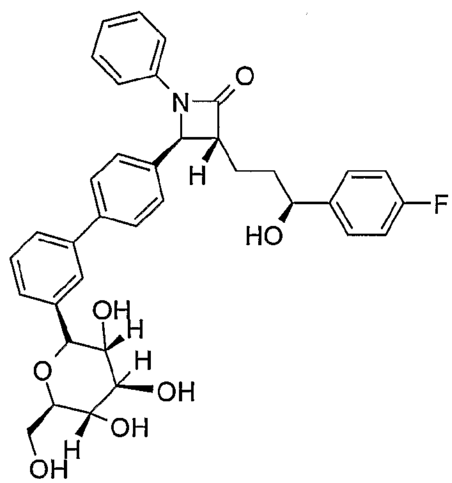
[00342] Example 63. Synthesized in the same manner as Example 62, but replacing 1,3 dibromobenzene with 1,4 dibromobenzene



(1S)-2,3,4,6-Tetra-O-acetyl-1,5-anhydro-1-(4-bromophenyl)-D-glucitol was obtained (45% yield, white wax). R_f 0.3 (40% ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.7, 2H), 5.31 (d, J = 9.3 Hz, 1H), 5.21 (t, J = 9.9 Hz, 1H), 5.09 (t, J = 9.6 Hz, 1H), 4.37 (d, J = 9.9 Hz, 1H), 4.12-4.33 (m,

2H), 3.83 (m, 1H), 2.09 (s, 3H), 2.06 (s, 3H), 2.00 (s, 3H), 1.83 (s, 3H) ppm; MS $[M+H]^+$ 488.4

[00343] Example 64. (1S)-1,5-Anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)-D-glucitol

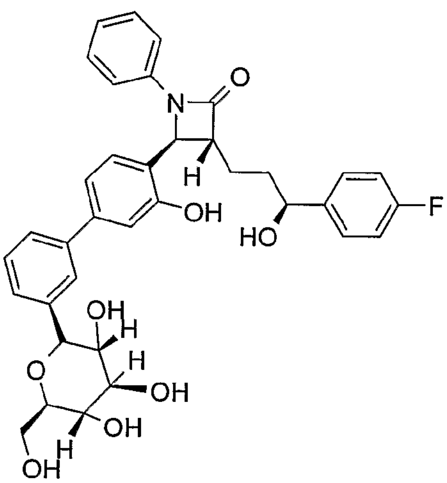


(3R,4S)-3-[(3S)-3-(4-Fluorophenyl)-3-hydroxypropyl]-1-phenyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]azetidin-2-one (51.3 mg, 0.102 mmol) and (1S)-2,3,4,6-tetra-O-acetyl-1,5-anhydro-1-(3-bromophenyl)-D-glucitol (35.5 mg, 0.073 mmol) were dissolved in 2.0 mL of toluene and 0.25 mL of ethanol. 0.075 mL of 4 N potassium carbonate was added to the mixture followed by 5.0 mg of tetrakis(triphenylphosphine)palladium(0). The entire reaction was degassed three times with argon then heated to reflux for 4 h. The reaction was cooled to room temperature, diluted with 5 mL of water , and extracted with ethyl acetate (3 x 25 mL). The organic layers were combine, dried over sodium sulfate, filtered, concentrated and purified by column chromatography (12 g silica gel, 5% to 95% ethyl acetate-hexane) to afford 10.5 mg (13%) of (1S)-2,3,4,6-tetra-O-acetyl-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)-D-glucitol as a clear oil.

[00344] (1S)-2,3,4,6-Tetra-O-acetyl-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)-D-glucitol (10.5 mg, 0.013 mmol) was dissolved in 0.30 mL of methanol and 0.30 mL of triethylamine followed by drop-wise addition of water (0.80 mL). The yellowish

mixture stirred at room temperature overnight. LCMS of the solution confirmed complete consumption of the starting material and formation of the fully deprotected material. The mixture was concentrated in vacuo, and purified by reverse-phase HPLC (Polaris C18-A 10μ 250 x 21.2 mm column, 30% to 95% acetonitrile-0.1% trifluoroacetic acid in water) to afford 2.8 mg (35%) of the desired (1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)-D-glucitol as a white powder; ^{1}H NMR (300 MHz, CD_3OD) δ 7.65 (d, J = 11.1 Hz, 2H), 7.54-7.23 (m, 10H), 7.05-6.89 (m, 3H), 4.61 (t, J = 6.3 Hz, 1H), 4.19 (d, J = 9.0 Hz, 1H), 3.87 (d, J = 10.7 Hz, 1H), 3.73 –3.63 (m, 1H), 3.49-3.36 (m, 3H) 3.22-3.18 (m, 2H), 1.89 (m, 4H) ppm; MS $[M-OH]^+$ 596.5

[00345] Example 65. (1S)-1,5-Anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucitol



(3R,4S)-4-(4-Bromo-2-{[tert-butyl(dimethyl)silyl]oxy}phenyl)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-1-phenylazetidin-2-one (0.42 g, 0.60 mmol) was dissolved in 15mL of dioxane in a sealed tube. Bis(pinacolato)diboron (0.17 g, 0.66 mmol), potassium acetate (0.18g, 1.83 mmol), and dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium(II) dichloromethane adduct (14.6 mg, 0.018 mmol) were added and the reaction was degassed with argon and heated to 85 °C for 24 h. The mixture was cooled to room temperature diluted with 50 mL of 1:1 ethyl acetate-hexane, washed with 100 mL of 0.1 N hydrochloric acid and 2 x 100 mL of brine. The organic layers were collected, partially

concentrated to half the volume, filtered through 10 g of silica gel, washed with 50 mL of ethyl acetate and concentrated in vacuo.

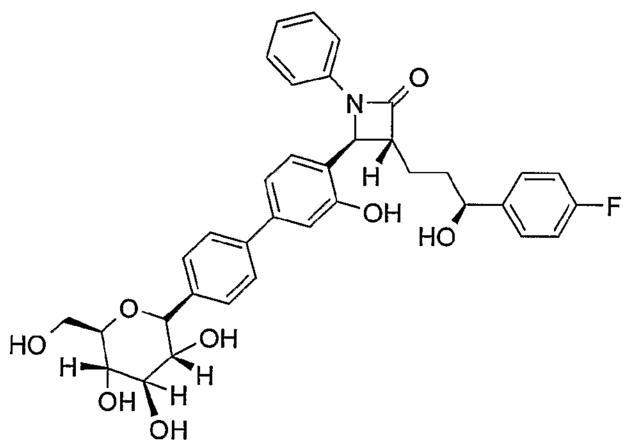
[00346] The resulting brown oil which is (3R,4S)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-[2-{[tert-butyl(dimethyl)silyl]oxy}-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-phenylazetidin-2-one was dissolved with (1S)-2,3,4,6-tetra-O-acetyl-1,5-anhydro-1-(3-bromophenyl)-D-glucitol in 4.0 mL of toluene and 0.5 mL of ethanol. 0.150 mL of 4 N potassium carbonate was added followed by 7 mg of tetrakis(triphenylphosphine)palladium(0). The entire reaction was degassed three times with argon then heated to reflux for 1.5 h. After this time the reaction was cooled to room temperature and diluted with 25 mL of water and extracted with 1:1 hexane-ethyl acetate (3 x 75 mL). The organic layers were combine, dried over sodium sulfate, filtered, concentrated and purified by column chromatography (12 g silica gel, 5% to 95% ethyl acetate-hexane) to afford 41.6 mg (27%) of (1S)-2,3,4,6-tetra-O-acetyl-1,5-anhydro-1-(3'-{[tert butyl(dimethyl)silyl]oxy}-4'-{(2S,3R)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)-D-glucitol as a clear oil.

[00347] This material was immediately dissolved in 0.80 mL of methanol and 0.80 mL of triethylamine followed by dropwise addition of water (2.3 mL). The yellow mixture was stirred at room temperature for 24 h, extracted with 1:1 ethyl acetate-hexane (3 x 100 mL), dried with sodium sulfate, and concentrated in vacuo to afford (1S)-1,5-anhydro-1-(3'-{[tert-butyl(dimethyl)silyl]oxy}-4'-{(2S,3R)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)-D-glucitol.

[00348] The final deprotection was accomplished by dissolving (1S)-1,5-anhydro-1-(3'-{[tert-butyl(dimethyl)silyl]oxy}-4'-{(2S,3R)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-4-yl)-D-glucitol in 5 mL of acetonitrile, and adding 2.5 mL of 48% hydrofluoric acid. The mixture stirred at room temperature of 1.5 h, neutralized with 70 mL of 1 N sodium hydroxide and 50 mL of 1 M sodium phosphate buffer pH 7.4, extracted into ethyl acetate (2 x 100 mL), washed with saturated sodium bicarbonate

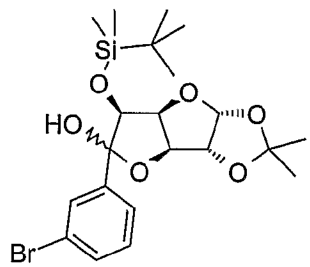
(2 x 25 mL), dried with sodium sulfate, filtered and concentrated in vacuo. The crude sample was purified by reverse-phase HPLC (Polaris C18-A 10μ 250 x 21.2 mm column, 30% to 95% acetonitrile-0.1% trifluoroacetic acid in water) to afford 7.9 mg (74%) of the desired (1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucitol as a white solid; [1]H NMR (300 MHz, CD_3OD) δ7.49 (dd, J = 6.6 Hz, 4H), 7.34-7.21 (m, 7H), 7.15 (d, J = 7.8 Hz, 1H), 7.07-6.97 (m, 5H), 5.13 (d, J = 2.1 Hz, 1H), 4.61 (m, 1H), 4.15 (d, J = 9.3 Hz, 1H) 3.90 (d, J = 12 Hz, 1H), 3.70 (m, 1H) 3.41 (m, 4H), 3.16 (m, 1H), 1.99-1.93 (m, 4H) ppm; MS $[M-OH]^+$ 612.6

[00349] Example 66. (1S)-1,5-Anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol



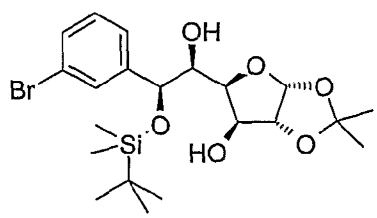
[00350] Obtained in a manner similar to Example 65, but using (1S)-2,3,4,6-tetra-O-acetyl-1,5-anhydro-1-(4-bromophenyl)-D-glucitol in place of (1S)-2,3,4,6-tetra-O-acetyl-1,5-anhydro-1-(3-bromophenyl)-D-glucitol. (1S)-1,5-Anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol (20 % yield, white solid). [1]H NMR (300 MHz, CD_3OD) δ 7.54 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.35-7.09 (m, 8H), 7.05-6.97 (m, 4H), 5.14 (d, *J* = 2.3 Hz, 1H), 4.63-4.59 (m, 1H), 4.17 (d, *J* = 9.5 Hz, 1H), 3.90 (dd, *J* = 11.8, 1.6 Hz, 1H), 3.71 (dd, *J* = 11.8, 4.9 Hz, 1H), 3.53-3.36 (m, 4H), 3.19-3.13 (m, 1H), 2.05-1.88 (m, 4H) ppm; $[\alpha]_D^{23}$ +1.7° (*c* 8.7, methanol).

[00351] Example 67. (2S/2R,3S,4S,6R,7R,8S)-3-O-tert-Butyldimethylsilyl-2,3,6,7-tetrahydroxy-6,7-O-isopropylidene-1,5-dioxa-2-(3-bromophenyl)-bicyclo[3.3.0]octane



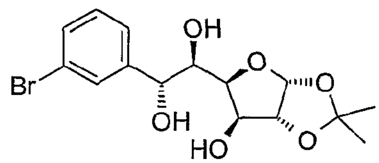
n-Butyllithium (31.5 mL, 41.0 mmol, 1.3 M hexane) was added via addition funnel to 1,3-dibromobenzene (9.64 g, 41.0 mmol, 4.94 mL) dissolved in anhydrous tetrahydrofuran (30 mL) at –78 °C over 30 min. The addition funnel was rinsed with anhydrous tetrahydrofuran (15 mL) and the reaction was allowed to stir for 30 min at –78 °C. To this solution was added 5-O-tert-butyldimethylsilyl-1,2-O-isopropylidene-α-D-glucuronolactone (4.5 g, 13.6 mmol) [prepared according to Tetrahedron Asymmetry 7:9, 2761, (1996)] dissolved in 30 mL of anhydrous tetrahydrofuran at –78 °C and the reaction stirred for 2 h. The reaction was quenched by the addition of saturated ammonium chloride (20 mL) followed by warming to room temperature. The reaction was poured into ethyl acetate (30 mL) and water (10 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated and purified by chromatography (1:1 diethyl ether-hexane) to afford a diastereomeric mixture of (2S/2R,3S,4S,6R,7R,8S)-3-O-tert-butyldimethylsilyl-2,3,6,7-tetrahydroxy-6,7-O-isopropylidene-1,5-dioxa-2-(3-bromophenyl)-bicyclo[3.3.0]octane (4.77 g, 72% yield) as a colorless viscous oil. R_f 0.51 (3:1 hexane-ethyl acetate)

[00352] Example 68. (6S)-6-C-(3-Bromophenyl)-6-O-[tert-butyl(dimethyl)silyl]-1,2-O-(1-methylethylidene)-α-D-glucofuranose



[00353] Sodium borohydride (11.1 mg, 0.29 mmol) was added to (2S/2R,3S,4S,6R,7R,8S)-3-O-tert-butyldimethylsilyl-2,3,6,7-tetrahydroxy-6,7-O-isopropylidene-1,5-dioxa-2-(3-bromophenyl)-bicyclo[3.3.0]octane dissolved in absolute ethanol (4 mL) at room temperature. The reaction was stirred at room temperature for 1 h. TLC analysis (3:1 hexane-ethyl acetate) indicated that all the starting lactol had been consumed. 1 mL of saturated ammonium chloride solution was added and the reaction was stirred until the effervescence ceased. The reaction was poured into ethyl acetate (30 mL) and water (10 mL) and the layers separated. The aqueous layer was extracted 2 x 20 mL with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated and purified by chromatography (3:1 hexane:ethyl acetate) to afford (6S)-6-C-(3-bromophenyl)-6-O-[tert-butyl(dimethyl)silyl]-1,2-O-(1-methylethylidene)- α-D-glucofuranose (125 mg, 88% yield) as a white waxy solid. mp 76-77 °C; R_f 0.24 (3:1 hexane:ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.17 (m, 4H), 5.95 (d, J = 3.6 Hz, 1H), 4.90 (s, 1H), 4.53 (d, J = 3.9 Hz, 1H), 4.32 (d, J = 2.7 Hz, 1H), 4.09 (dd, J = 2.7 Hz, J = 8.4 Hz, 1H), 3.75 (d, J = 7.2 Hz, 1H), 2.76-2.68 (br s, 2H), 1.46 (s, 3H), 1.31 (s, 3H), 0.92 (s, 9H), 0.11 (s, 3H), -0.10 (s, 3H) ppm

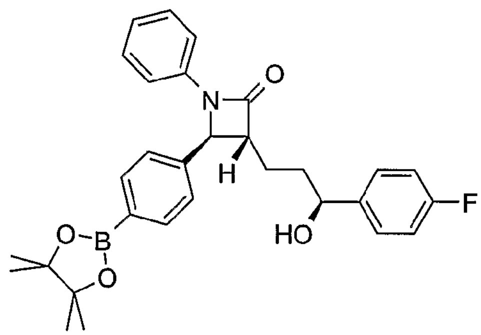
[00354] Example 69. (6R)-6-C-(3-Bromophenyl)-1,2-O-(1-methylethylidene)-α-D-glucofuranose



[00355] Tetrabutylammonium fluoride (1 M in tetrahydrofuran, 3.14 mL) was added dropwise to (2S/2R,3S,4S,6R,7R,8S)-3-O-tert-butyldimethylsilyl-2,3,6,7-tetrahydroxy-6,7-O-isopropylidene-1,5-dioxa-2-(3-bromophenyl)-bicyclo[3.3.0]octane (1.53 g, 3.14 mmol) and glacial acetic acid (188.4 mg, 3.14 mmol, 180 μL) in anhydrous tetrahydrofuran (30 mL) at 0 °C. The reaction was stirred for 30 min at 0 °C then warmed to room temperature and stirred an additional 30 min. TLC analysis (3:1 hexane-ethyl acetate) indicated that the starting material had been completely consumed. The reaction was poured into ethyl acetate (30 mL), washed with saturated sodium bicarbonate (10 mL) and brine (2 x 10 mL). The aqueous layer was back extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated and purified by chromatography (35 g, 40% ethyl acetate-hexane isocratic) to afford (2S/2R,3S,4S,6R,7R,8S)-2,3,6,7-tetrahydroxy-6,7-O-isopropylidene-1,5-oxa-2-(3-bromophenyl)-bicyclo[3.3.0]octane (1.146 g, 98% yield) as a white solid; R_f 0.18 (3:1 hexane-ethyl acetate)

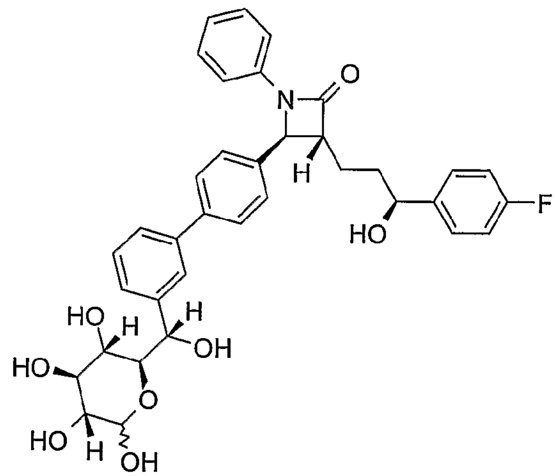
[00356] Sodium borohydride (116 mg, 3.1 mmol) was added to (2S/2R,3S,4S,6R,7R,8S)-2,3,6,7-tetrahydroxy-6,7-O-isopropylidene-1,5-oxa-2-(3-bromophenyl)-bicyclo[3.3.0]octane (1.15 g, 3.1 mmol) dissolved in absolute ethanol (5 mL) at room temperature. The reaction was stirred at room temperature for 1 h. TLC analysis (2:1 ethyl acetate-hexane) indicated that all the starting lactol had been consumed. 1 mL of saturated ammonium chloride solution was added and the reaction stirred until the effervescence ceased. The reaction was poured into ethyl acetate (30 mL) and water (10 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated and purified by chromatography (2:1 ethyl acetate-hexane to elute the first diastereomer then 100% ethyl acetate) to afford (6R)-6-C-(3-bromophenyl)-1,2-O-(1-methylethylidene)- α-D-glucofuranose (511 mg, 89% yield) as a white solid; mp 172-173 °C; R_f 0.19 (2:1 ethyl acetate-hexane); ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$) δ 7.62-7.61 (m, 1H), 7.42-7.38 (m, 1H), 7.21 (t, J = 7.5 Hz, 1H), 5.94 (d, J = 3.9 Hz, 1H), 4.86 (d, J = 4.5 Hz, 1H), 4.48 (d, J = 3.3 Hz, 1H), 4.24 (d, J = 2.4 Hz, 1H), 4.14-4.10 (m, 1H), 3.79-3.74 (m, 1H), 1.38 (s, 3H), 1.30 (s, 3H) ppm

[00357] Example 70. (3R,4S)-3-[(3S)-3-(4-Fluorophenyl)-3-hydroxypropyl]-1-phenyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]azetidin-2-one



[00358] (3R,4S)-4-(4-Bromophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one (45.1 mg, 0.10 mmol), bis(pinacolato)diboron (27.7 mg, 0.11 mmol), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (2.4 mg, 0.003 mmol), and potassium acetate (29.7 mg, 0.30 mmol) were dissolved in anhydrous dimethyl sulfoxide (600 μL). The vessel was evacuated and flushed with argon three times then sealed and heated at 80 °C for 16 h. LCMS analysis indicated that some starting material remained so an additional aliquot of catalyst and bis(pinacolato)diboron were added, the solution degassed and heating continued for 2 h. The reaction was diluted into dichloromethane (30 mL) and filtered through a plug of Celite®. The filtrate was washed 2 x 10 mL with water. The combined aqueous washed were back extracted with 3 x 10 mL dichloromethane. The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The product was purified by chromatography (12 g silica gel, 20-50% ethyl acetate-hexane) to afford (3R,4S)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]azetidin-2-one (41.9 mg, 85% yield) as a tan foam; R_f (1:1 hexane-ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 8.1 Hz, 1H), 7.35-7.18 (m, 9 H), 7.04-6.97 (m, 3H), 4.70 (t, J = 5.7 Hz, 1H), 4.65 (d, J = 2.1 Hz, 1H), 3.08 (dt, J = 7.7, 2.5, 1H), 2.02-1.87 (m, 4H), 1.33 (s, 12H) ppm

[00359] Example 71. (6S)-6-C-(4'-{(2S,3R)-3-[(3S)-3-(4-Fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)-D-glucopyranose

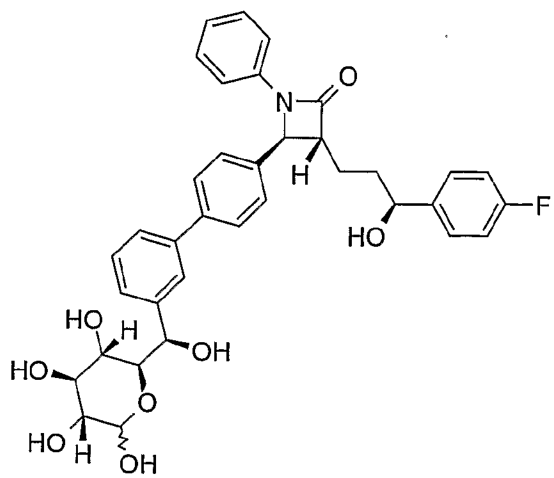


[00360] (3R,4S)-3-[(3S)-3-(4-Fluorophenyl)-3-hydroxypropyl]-1-phenyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]azetidin-2-one (26.8 mg, 0.05 mmol), (6S)-6-C-(3-bromophenyl)-6-O-[tert-butyl(dimethyl)silyl]-1,2-O-(1-methylethylidene)- α-D-glucofuranose (18.1 mg, 0.04 mmol), and potassium carbonate (40 μL, 4 N aqueous) were dissolved in 1:1 toluene:ethanol (1 mL total volume). The solution was degassed by evacuating the vessel and flushing with argon three times. Tetrakis(triphenylphosphine)palladium(0) (2.2 mg, 0.002 mmol) was added and the solution was degassed twice. The reaction was heated at 85 °C for 1 h. LCMS and TLC (1:1 hexane-ethyl acetate) analysis indicated consumption of the starting glycoside. The reaction was diluted into ethyl acetate (30 mL) and washed with water (2 x 10 mL). The combined aqueous washes were back extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated in vacuo and purified by chromatography (12 g silica gel, 20-50% ethyl acetate-hexane) to afford (6S)-6-O-[tert-butyl(dimethyl)silyl]-6-C-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)-1,2-O-(1-methylethylidene)- α-D-glucofuranose (13.5 mg, 45% yield) as a white foam; R_f 0.23 (1:1 hexane-ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$) δ 7.58-7.22 (m, 13H), 7.07-6.98 (m, 4H), 5.97 (d, J = 3.9 Hz, 1H),

4.98 (d, J = 2.4 Hz, 1H), 4.73 (t, J = 6.3 Hz, 1H), 4.69 (d, J = 2.1 Hz, 1H), 4.54 (d, J = 3.9 Hz, 1H), 4.37 (d, J = 2.4 Hz, 1H), 3.87-3.86 (m, 1H), 3.13-3.09 (m, 1H), 2.04-1.86 (m, 4H), 1.43 (s, 3H), 1.31 (s, 3H), 0.94 (s, 9H), 0.12 (s, 3H), -0.09 (s, 3H) ppm

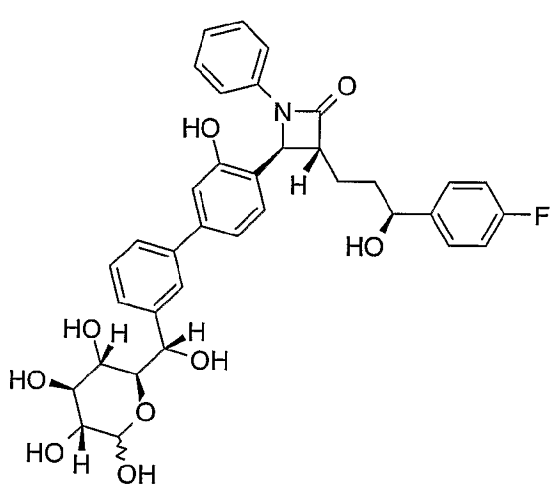
[00361] (6S)-6-O-[tert-Butyl(dimethyl)silyl]-6-C-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)-1,2-O-(1-methylethylidene)- α-D-glucofuranose (13.5 mg, 0.017 mmol) was dissolved in acetonitrile (5 mL) in a polypropylene centrifuge tube. 48% Hydrofluoric acid (500 μL) was added at room temperature and the reaction was stirred for 16 h monitoring by LCMS. Upon completion, 1 equivalent of solid sodium carbonate (1.27 g, 12 mmol) was added and just enough water to dissolve the solid. The reaction was diluted into ethyl acetate (20 mL) and the layers separated. The aqueous solution was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with saturated sodium carbonate (2 x 10 mL), dried over anhydrous sodium sulfate, filtered, concentrated in vacuo and purified by reverse-phase HPLC (Polaris C18-A 10μ 250 x 21.2 mm column, 30% to 95% acetonitrile-0.1% trifluoroacetic acid in water) to afford (6S)-6-C-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)-D-glucopyranose (5.5 mg, 51%); ^1H NMR (300 MHz, $CDCl_3/CD_3OD$) δ 7.64-7.58 (m, 2H), 7.48-7.21 (m, 12H), 7.08-6.98 (m, 3H), 5.12-5.07 (m, 1.4H), 4.73 (d, J = 2.4 Hz, 1H), 4.66 (t, J = 5.7 Hz, 1H), 4.39 (d, J = 7.5 Hz, 0.6H), 4.00 (dd, J = 1.5 Hz, J = 9.6 Hz, 0.6H), 3.76-3.56 (m), 3.23-3.10 (m, 1.5H), 2.01-1.90 (m, 4H) ppm; MS $[M+H]^+$ 630.0

[00362] Example 72. (6R)-6-C-(4'-{(2S,3R)-3-[(3S)-3-(4-Fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)-D-glucopyranose



[00363] Obtained in a manner similar to Example 71 but using as starting materials the products from Examples 68 and 70. (6R)-6-C-(4'-{(2S,3R)-3-[(3S)-3-(4-Fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)-D-glucopyranose (2.4 mg, 53% yield); ^{1}H NMR (300 MHz, $CDCl_3$/ 0.1% CD_3OD) δ 7.64-7.58 (m, 2H), 7.49-7.23 (m, 12H), 7.08-6.98 (m, 3H), 5.06 (d, J = 3.6 Hz, 0.6H), 4.91 (d, J = 6.0 Hz, 1H), 4.72 (d, J = 4.8 Hz, 1H), 4.66 (t, J = 5.4 Hz, 1H), 4.42 (d, J = 7.8 Hz, 0.4H), 4.07-4.02 (m, 1H), 3.69-3.66 (m, 1H), 3.16-3.11 (m, 1H), 1.96-1.91 (m, 4H) ppm; MS $[M+H]^+$ 630.0

[00364] Example 73. (6S)-6-C-(4'-{(2S,3R)-3-[(3S)-3-(4-Fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucopyranose

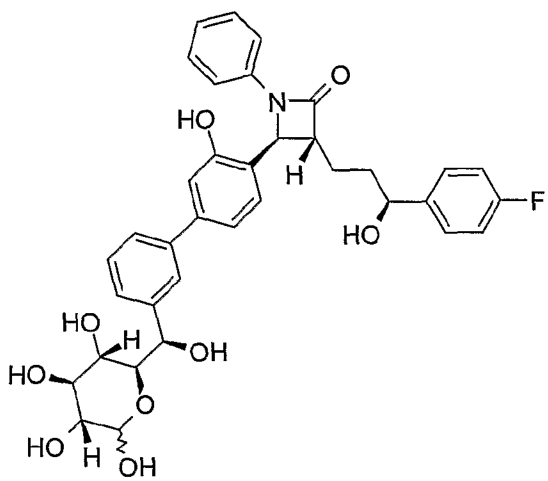


[00365] (3R,4S)-3-[(3S)-3-{[tert-Butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-[2-{[tert-butyl(dimethyl)silyl]oxy}-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-phenylazetidin-2-one (53.0 mg, 0.07 mmol), (6S)-6-C-(3-bromophenyl)-6-O-[tert-butyl(dimethyl)silyl]-1,2-O-(1-methylethylidene)- α-D-glucofuranose (24.1 mg, 0.05 mmol), and potassium carbonate (50 μL, 4 N aqueous solution) were dissolved in 1:1 toluene:ethanol (1 mL total volume). The solution was degassed by evacuating the vessel and flushing with argon three times. Tetrakis(triphenylphosphine)palladium (4.0 mg, 0.003 mmol) was added and the solution degassed twice. The reaction was heated at 85 °C for 1 h. LCMS and TLC (1:1 hexane-ethyl acetate) analysis indicated consumption of the starting glycoside. The reaction was diluted into ethyl acetate (30 mL) and washed with water (2 x 10 mL). The combined aqueous washes were back extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated in vacuo, and purified by chromatography (12 g silica gel, 5-50% ethyl acetate-hexane) to afford (6S)-6-O-[tert-butyl(dimethyl)silyl]-6-C-(4'-{(2S,3R)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-1,2-O-(1-methylethylidene)- α-D-glucofuranose (10.5 mg, 20% yield) as a white foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.18 (m, 13H), 7.05-6.93 (m, 3H), 5.97 (d, J = 3.9 Hz, 1H), 5.03 (d, J = 2.1 Hz, 1H), 4.95 (d, J = 2.4 Hz, 1H), 4.67 (m, 1H), 4.56 (t, J = 4.8 Hz, 1H), 4.38 (m, 1H), 4.10 (dd, J = 7.6, 3.0Hz, 1H), 3.87 (m, 1H), 3.12 (m, 1H),1.94-1.89 (m, 4H), 1.44 (s, 3H), 1.31 (s, 3H), 0.93 (s, 9H), 0.86 (s, 9H), 0.11 (s, 3H), 0.01 (s, 3H), -0.11 (s, 3H), -0.16 (s, 3H) ppm

[00366] (6S)-6-O-[tert-Butyl(dimethyl)silyl]-6-C-(4'-{(2S,3R)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-1,2-O-(1-methylethylidene)- α-D-glucofuranose was dissolved in acetonitrile (5 mL) in a polypropylene centrifuge tube. 48% Hydrofluoric acid (750 μL) was added at room temperature and the reaction stirred for 16 h monitoring progress by LCMS. Upon completion, 1 equivalent of solid sodium carbonate (1.91 g, 18 mmol) was added and just enough water to dissolve the solid. The reaction was diluted into ethyl acetate (20 mL) and the layers separated. The aqueous solution was

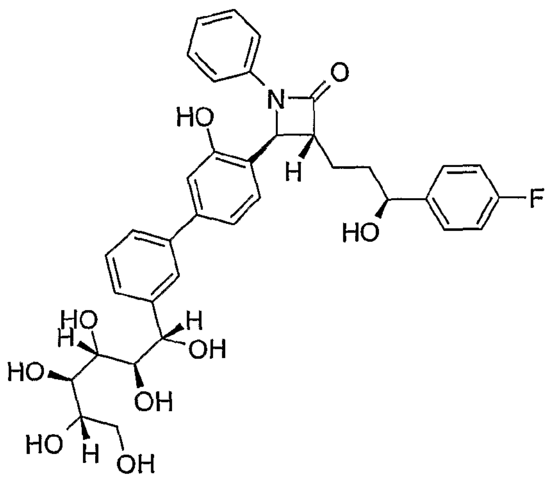
extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with saturated sodium carbonate (2 x 10 mL), dried over anhydrous sodium sulfate, filtered, concentrated in vacuo and purified by reverse-phase HPLC (Polaris C18-A 10μ 250 x 21.2 mm column, 30% to 95% acetonitrile-0.1% trifluoroacetic acid in water) to afford (6S)-6-C-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucopyranose (17.8 mg); ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$) δ 7.52-6.83 (m, 16H), 5.05-5.00 (m, 2H), 4.50 (m, 1H), 4.34 (m, 1H), 3.94 (m, 1H), 3.72-3.59 (m, 2H), 2.91 (m, 1H), 1.95-1.77 (m, 4H) ppm; MS $[M-OH]^+$ 627.8

[00367] Example 74. (6R)-6-C-(4'-{(2S,3R)-3-[(3S)-3-(4-Fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucopyranose



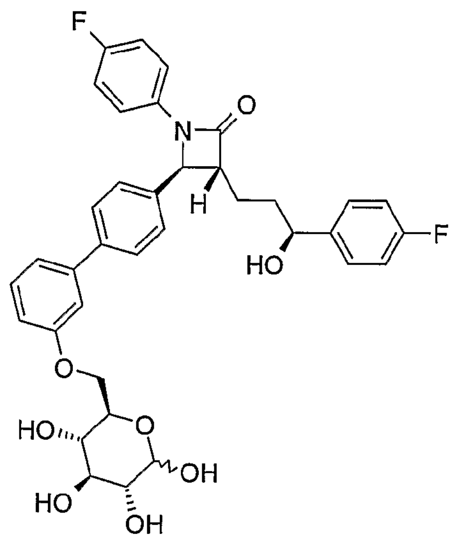
[00368] Obtained in a manner similar to Example 73. Purified by reverse-phase HPLC (Polaris C18-A 10μ 250 x 21.2 mm column, 30% to 95% acetonitrile-0.1% trifluoroacetic acid in water) to afford (6R)-6-C-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucopyranose (4.1 mg, 70% yield); ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$) δ 7.55-6.90 (m, 16H), 5.08-2.06 (m, 1H), 5.01-5.00 (m, 1H), 4.86 (d, J = 4.5 Hz, 1H), 4.60 (t, J = 5.1 Hz, 1H), 4.39 (d, J = 8.1 Hz, 1H), 4.02-3.97 (m, 1H), 3.70-3.64 (m, 1H), 3.52-3.49 (m, 1H), 1.96-1.85 (m, 4H) ppm; MS $[M-OH]^+$ 627.8

[00369] Example 75. (6S)-6-C-(4'-{(2S,3R)-3-[(3S)-3-(4-Fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucitol



[00370] (6S)-6-C-(4'-{(2S,3R)-3-[(3S)-3-(4-Fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucopyranose (7.1 mg, 0.01 mmol) was dissolved in 80:20 acetonitrile-water (1 mL). Sodium borohydride (0.4 mg, 0.01 mmol) was added at room temperature and the reaction was stirred for 30 min monitoring by LCMS. Upon completion, the reaction was diluted with 80:20 acetonitrile:water (3 mL) then filtered through a Whatman 0.45 μM glass microfiber filter and purified by reverse-phase HPLC (Polaris C18-A 10μ 250 x 21.2 mm column, 30% to 95% acetonitrile-0.1% trifluoroacetic acid in water) to afford (6S)-6-C-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucitol (1.4 mg, 22% yield). ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$) δ 7.37-6.89 (m, 16H), 5.08 (d, J = 2.4 Hz, 1H), 4.97-4.95 (m, 1H), 4.60 (t, J = 6.0 Hz, 1H), 3.92 (m, 1H), 3.76-3.56 (m, 6H), 2.01-1.82 (m, 4H) ppm; MS $[M-OH]^+$ 629.8

[00371] Example 76. 6-O-(4'-{(2S,3R)-1-(4-Fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)-D-glucopyranose



[00372] Diethylazodicarboxylate (192.4 mg, 1.11 mmol, 172 μL) was added drop-wise at 0 °C to 1,2,3,4-tetra-O-acetyl-□-D-glucopyranose (350.0 mg, 1.01 mmol), 3-bromophenol (174.0 mg, 1.11 mmol), and triphenylphosphine (115.0 mg, 0.44 mmol) dissolved in dry tetrahydrofuran (2 mL). The reaction was stirred for 16 h warming to room temperature. The reaction was diluted into diethyl ether (30 mL) and washed with 5% sodium bisulfate (2 x 10 mL). The separated organic solution was dried over anhydrous sodium sulfate, filtered, concentrated in vacuo and purified by chromatography (20% ethyl acetate-dichloromethane) to afford 1,2,3,4-tetra-O-acetyl-6-O-(3-bromophenyl)-□-D-glucopyranose (357 mg, 71% yield)

[00373] Triethylamine (1 mL) was added at room temperature to 1,2,3,4-tetra-O-acetyl-6-O-(3-bromophenyl)-□-D-glucopyranose (200 mg, 0.40 mmol) dissolved in 5:1methanol-water (6 mL). The reaction progress was monitored by LCMS and TLC (20% ethyl acetate-dichloromethane). Upon completion, the solvents were removed in vacuo to afford 6-O-(3-bromophenyl)-□-D-glucopyranose which was carried on without further purification.

[00374] tert-Butyldimethylsilyl trifluoromethanesulfonate (442 mg, 1.67 mmol, 383 μL) was added dropwise at 0 °C to 6-O-(3-bromophenyl)-β-D-glucopyranose and 4-dimethylaminopyridine (219 mg, 1.79 mmol) dissolved in dichloromethane (3 mL). The reaction was stirred for 16 h warming to room temperature. The reaction was diluted into dichloromethane (30 mL) and washed with 5% sodium bisulfate (2 x 10

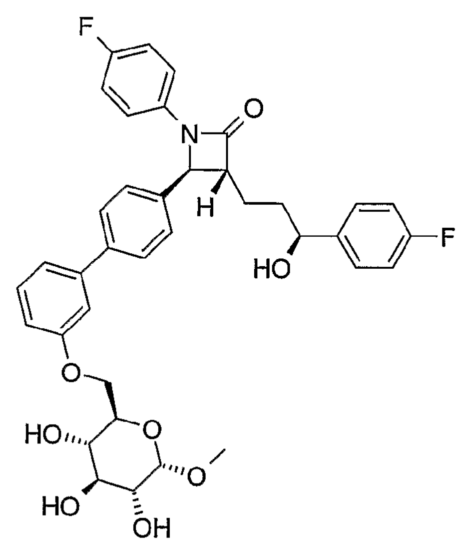
mL). The separated organic solution was dried over anhydrous sodium sulfate, filtered, concentrated in vacuo and purified by chromatography (50% ethyl acetate:hexane) to afford a 6-O-(3-bromophenyl)-β-D-glucopyranose bis-O-[tert-butyl(dimethyl)silyl] ether (98.9 mg, 44% yield); $R_f = 0.14$ (50% ethyl acetate-hexane)

[00375] (3R,4S)-1-(4-Fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]azetidin-2-one (141.5 mg, 0.27 mmol), 6-O-(3-bromophenyl)-β-D-glucopyranose bis-O-[tert-butyl(dimethyl)silyl] ether (98.9 mg, 0.18 mmol), and potassium carbonate (175 μL, 2 M aqueous solution) were dissolved in 1:1 toluene-ethanol (1 mL total volume). The solution was degassed by evacuating the vessel and flushing with argon three times. Tetrakis(triphenylphosphine)palladium (10.0 mg, 0.009 mmol) was added and the solution degassed twice. The reaction was heated at 85 °C for 1 h. LCMS and TLC (1:1 hexane-ethyl acetate) analysis indicated consumption of the starting glycoside. The reaction was diluted into ethyl acetate (30 mL) and washed with water (2 x 10 mL). The combined aqueous washes were back extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated in vacuo and purified by chromatography (12 g silica gel, 50% ethyl acetate-hexane) to afford 6-O-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)-β-D-glucopyranose bis-O-[tert-butyl(dimethyl)silyl] ether (113 mg, 74% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 7.8 Hz, 2H), 7.36-7.10 (m, 8H), 7.01-6.80 (m, 6H), 4.70 (t, J = 5.4 Hz, 1H), 4.64 (d, J = 1.8 Hz, 1H), 4.56 (d, J = 6.9 Hz, 1H), 4.35-4.32 (m, 1H), 4.16-4.07 (m, 1H), 3.68-3.58 (m, 2H), 3.51-3.46 (m, 1H), 3.38-3.32 (m, 1H), 3.11-3.09 (m, 1H), 1.98-1.88 (m, 4H), 0.91 (s, 9H), 0.91 (s, 9H), 0.14 (s, 6H), 0.13 (s, 6H) ppm

[00376] 6-O-(4'-{(2S,3R)-1-(4-Fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)- α-D-glucopyranose bis-O-[tert-butyl(dimethyl)silyl] ether (82.3 mg, 0.09 mmol) was dissolved in acetonitrile (10 mL) in a polypropylene centrifuge tube. 48% Hydrofluoric acid (1 mL) was added at room temperature and the reaction monitored by LCMS. Upon completion, 1 equivalent of solid sodium carbonate (2.54 g, 24 mmol) was added and just enough

water to dissolve the solid. The reaction was diluted into ethyl acetate (20 mL) and the layers separated. The aqueous solution was extracted with ethyl acetate (3 x10 mL). The combined organic extracts were washed with saturated sodium carbonate (2 x 10 mL), dried over anhydrous sodium sulfate, filtered, concentrated in vacuo and purified by reverse phase preparative HPLC (Polaris C18-A 10μ 250 x 21.2 mm column, 30% to 95% acetonitrile-0.1% trifluoroacetic acid in water) to afford 6-O-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)- α-D-glucopyranose (54.3 mg, 89% yield). ^{1}H NMR (300 MHz, $CDCl_3$/1% CD_3OD) δ 7.58 (d, J = 7.8 Hz, 2H), 7.39-7.24 (m, 7H), 7.17-7.14 (m, 2H), 7.04-6.92 (m, 5H), 5.23 (d, J = 3.9 Hz, 0.6H), 4.71 (d, J = 1.8 Hz, 1H), 4.66 (t, J = 5.7 Hz, 1H), 4.58 (d, J = 8.1 Hz, 0.4H), 4.40-4.30 (m, 1H), 4.25-4.14 (m, 1H), 3.57-3.48 (m, 2H), 3.16-3.11 (m, 1H), 2.04-1.85 (m, 4H) ppm; MS $[M-OH]^+$ 630.0

[00377] Example 77. Methyl 6-O-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)- α-D-glucopyranoside



[00378] Diethylazodicarboxylate (76.2 mg, 0.44 mmol, 68 μL) was added drop-wise to methyl 2,3,4-tri-O-benzyl- α-D-glucopyranoside (184.8 mg, 0.40 mmol), 3-bromophenol (72.3 mg, 0.42 mmol), and triphenylphosphine (115.0 mg, 0.44 mmol)

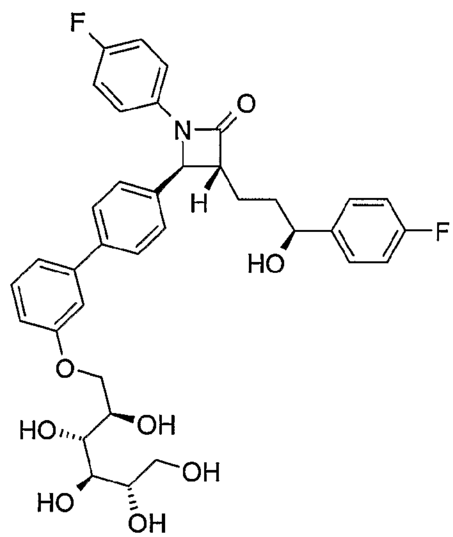
dissolved in dry tetrahydrofuran (2 mL) at 0 °C. The reaction was stirred for 16 h warming to room temperature. The reaction was diluted into dichloromethane (30 mL) and washed with 5% sodium bisulfate (2 x 10 mL). The separated organic solution was dried over anhydrous sodium sulfate, filtered, concentrated in vacuo and purified by chromatography (20% ethyl acetate-dichloromethane) to afford methyl 2,3,4-tri-O-benzyl-6-O-(3-bromophenyl)- α-D-glucopyranoside (216 mg, 87% yield)

[00379] (3R,4S)-1-(4-Fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]azetidin-2-one (64.1 mg, 0.12 mmol), methyl 2,3,4-tri-O-benzyl-6-O-(3-bromophenyl)-D-glucopyranoside (54.6 mg, 0.09 mmol), and potassium carbonate (88 μL, 2 M aqueous solution) were dissolved in 1:1 toluen-ethanol (1 mL total volume). The solution was degassed by evacuating the vessel and flushing with argon three times. Tetrakis(triphenylphosphine)palladium (5.1 mg, 0.004 mmol) was added and the solution degassed twice. The reaction was heated at 85 °C for 1 h. LCMS and TLC (1:1 hexane-ethyl acetate) analysis indicated consumption of the starting glycoside. The reaction was diluted into ethyl acetate (30 mL) and washed with water (2 x 10 mL). The combined aqueous washes were back extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated in vacuo and purified by chromatography (12 g silica gel, 20% to 50% ethyl acetate-hexane) to afford methyl 2,3,4-tri-O-benzyl-6-O-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)- α-D-glucopyranoside (70.0 mg, 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 8.1 Hz, 2H), 7.39-6.84 (m, 29H), 5.01 (d, J = 10.8 Hz, 1H), 4.89-4.80 (m, 3H), 4.73-4.64 (m, 4H), 4.52 (d, J = 11.1 Hz, 1H), 4.15-4.12 (m, 2H), 4.08-4.-1 (m, 1H), 3.94-3.90 (m, 1H), 3.77-3.71 (m, 1H), 3.62 (dd, J = 3.6 Hz, J = 9.6 Hz, 1H), 3.39 (s, 3H), 3.13-3.10 (m, 1H), 2.03-1.89 (m, 4H) ppm.

[00380] Methyl 2,3,4-tri-O-benzyl-6-O-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)- α-D-glucopyranoside (70 mg, 0.08 mmol) was dissolved in absolute ethanol (3 mL). 10% Pd/C (wet, 14% w/w) was added and the vessel sealed. The solution was degassed by evacuation and flushing with hydrogen gas at balloon pressure. The reaction was

monitored by TLC (1:1 hexane-ethyl acetate). Upon completion, the catalyst was filtered by passing through a plug of Celite® and washing with additional ethanol. The filtrate was concentrated in vacuo and purified by preparative HPLC (Polaris C18-A 10μ 250 x 21.2 mm column, 30% to 95% acetonitrile-0.1% trifluoroacetic acid in water) affording methyl 6-O-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)- α-D-glucopyranoside (18.1 mg, 36% yield); ^{1}H NMR (300 MHz, $CDCl_3$/1% CD_3OD) δ 7.58 (d, J = 8.4 Hz, 2H), 7.38-7.23 (m, 7H), 7.17-7.14 (m, 2H), 7.04-6.92 (m, 5H), 4.80 (d, J = 3.9 Hz, 1H), 4.70 (d, J = 2.4 Hz, 1H), 4.67 (t, J = 5.7 Hz, 1H), 4.37-4.33 (m, 1H), 4.26-4.21 (m, 1H), 3.92-3.87 (m, 1H), 3.74-3.45 (m, 3H), 3.42 (s, 3H), 3.18-3.10 (m, 1H), 2.01-1.88 (m, 4H) ppm; MS $[M-OH]^+$ 644.0

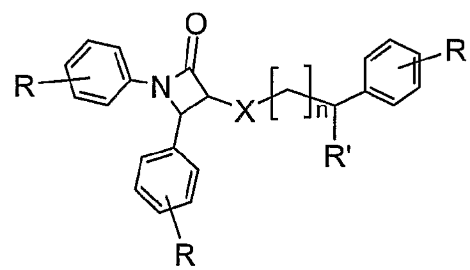
[00381] Example 78. 6-O-(4'-{(2S,3R)-1-(4-Fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)-D-glucitol



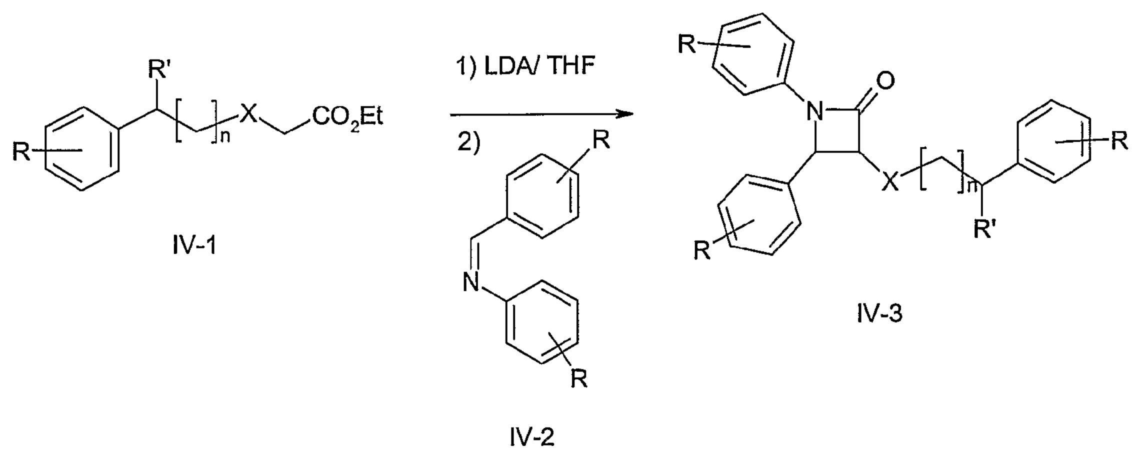
[00382] Sodium borohydride (1.6 mg, 0.04 mmol) was added to 6-O-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)-D-glucopyranose (26.3 mg, 0.04 mmol) dissolved in 80:20 acetonitrile-water (1 mL) at room temperature. The reaction was stirred for 10 min at room temperature monitoring by LCMS. Upon completion, the reaction was diluted with 50:50 acetonitrile:water (3 mL) and filtered through a Whatman 0.45 μM glass

microfiber filter then purified by preparative HPLC (Polaris C18-A 10μ 250 x 21.2 mm column, 30% to 95% acetonitrile-0.1% trifluoroacetic acid in water) affording 6-O-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)-D-glucitol (21.2 mg, 80% yield). ^{1}H NMR (300 MHz, $CDCl_3$/1% CD_3OD) δ 7.58 (d, J = 8.1 Hz, 2H), 7.39-7.24 (m, 7H), 7.17-7.15 (m, 2H), 7.04-6.92 (m, 5H), 4.71 (d, J = 2.1 Hz, 1H), 4.68 (t, J = 6.3 Hz, 1H), 4.31-4.27 (m, 1H), .19-4.14 (m, 1H), 4.08-4.02 (m, 1H), 3.97-3.95 (m, 1H), 3.86-3.65 (m, 4H), 3.14-3.12 (m, 1H), 2.01-1.88 (m, 4H) ppm; MS $[M+HCO_2^-]^-$ 694.0

Scheme IV



[00383] Illustrated in Scheme IV is the general method for the preparation of cholesterol absorption inhibitors of general formula IV-3. Imines IV-2 are made by refluxing anilines with the appropriate aldehydes in isopropanol. Condensation of imine IV-2 with the ester enolate of compound IV-1 affords the azetidinone IV-3. In the case where X is sulfur, one equivalent of an appropriate oxidizing agent such as MCPBA can be used to convert to the sulfoxide, two equivalents can be used to synthesize the sulfone. Where X is nitrogen, one equivalent of an appropriate oxidizing agent can be used to convert the secondary amine to a hydroxylamine (following deprotection).



[00384] The following examples were also prepared according to the methods described above:

[00385] Example 81. (3R,4S)-4-(3',4'-dimethoxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one

[00386] Example 82. (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[3'-(methylthio)biphenyl-4-yl]azetidin-2-one

[00387] Example 83. (3R,4S)-4-[3'-(dimethylamino)biphenyl-4-yl]-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one

[00388] Example 84. (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4'-vinylbiphenyl-4-yl)azetidin-2-one

[00389] Example 85. 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-5-methoxybiphenyl-2-carbaldehyde

[00390] Example 86. (3R,4S)-4-(3'-aminobiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one

[00391] Example 87. (3R,4S)-4-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one

[00392] Example 88. (4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-4-yl)acetic acid

[00393] Example 89. methyl 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-4-carboxylate

[00394] Example 90. (3R,4S)-4-(3',5'-dimethylbiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one

[00395] Example 91. (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[4-(2-naphthyl)phenyl]azetidin-2-one

[00396] Example 92. (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[3'-(trifluoromethyl)biphenyl-4-yl]azetidin-2-one

[00397] Example 93. (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-methylbiphenyl-4-yl)azetidin-2-one

[00398] Example 94. (3R,4S)-4-(4'-fluoro-3'-methylbiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one

[00399] Example 95. 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl β-L-glucopyranoside

[00400] Example 96. (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(2',3',4'-trimethoxybiphenyl-4-yl)azetidin-2-one

[00401] Example 97. (3R,4S)-4-(2',4'-dimethoxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one

[00402] Example 98. (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(2'-methylbiphenyl-4-yl)azetidin-2-one

[00403] Example 99. 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-4-carbaldehyde

[00404] Example 100. (3R,4S)-4-(3'-ethoxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one

[00405] Example 101. (3R,4S)-4-(4'-ethoxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one

[00406] Example 102. (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4'-hydroxy-3'-methoxybiphenyl-4-yl)azetidin-2-one

[00407] Example 103. (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-propoxybiphenyl-4-yl)azetidin-2-one

[00408] Example 104. 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-5-hydroxybiphenyl-2-carbaldehyde

[00409] Example 105. (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-isopropoxybiphenyl-4-yl)azetidin-2-one

[00410] Example 106. 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-4-hydroxybiphenyl-3-carboxylic acid

[00411] Example 107. (3R,4S)-4-(3',5'-dimethoxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one

[00412] Example 108. (3R,4S)-4-(2',4'-dihydroxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one

[00413] Example 109. (3R,4S)-4-(3'-butoxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one

[00414] Example 110. 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-3-hydroxybiphenyl-4-carboxylic acid

[00415] Example 111. (3R,4S)-4-(3'-fluoro-5'-methoxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one

[00416] Example 112. (3R,4S)-4-(3'-fluoro-5'-hydroxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one

[00417] Example 113. (1S)-1,5-anhydro-1-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)-L-glucitol

[00418] Example 114. (3R,4S)-4-(3',5'-dihydroxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one

[00419] Example 115. (4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)boronic acid

[00420] Example 116. (1R)-1,5-anhydro-1-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-4-yl)-L-glucitol

[00421] Example 117. 2,6-anhydro-1-deoxy-1-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)-D-glycero-D-gulo-heptitol

[00422] Example 118. 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-sulfonic acid

[00423] Example 119. (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-mercaptobiphenyl-4-yl)azetidin-2-one

[00424] Example 120. 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-N,N,N-trimethylbiphenyl-3-aminium

[00425] Example 121. (3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one

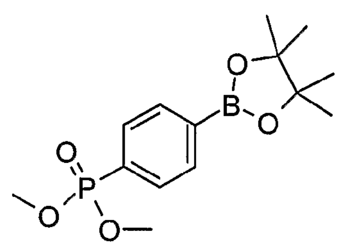
[00426] Example 122. (4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)phosphonic acid

[00427] Example 123. (3R,4S)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[3-hydroxy-3'-(methylsulfonyl)biphenyl-4-yl]-1-phenylazetidin-2-one

[00428] Example 124. (3R,4S)-1-biphenyl-4-yl-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-hydroxybiphenyl-4-yl)azetidin-2-one

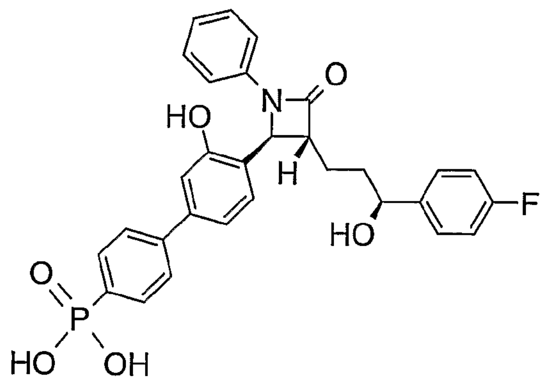
[00429] Example 125. (3R,4S)-4-(3,4'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one.

[00430] Example 126. Dimethyl [4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]phosphonate



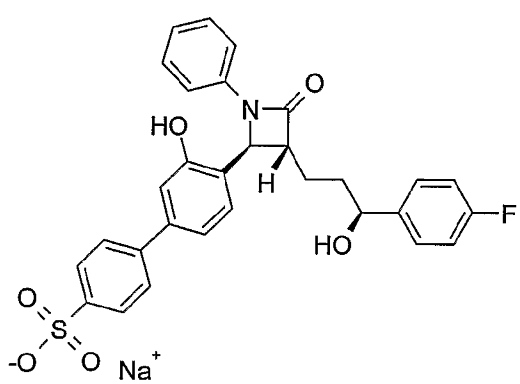
prepared in analogous manner to dimethyl [3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]phosphonate (Example 60) starting with 4-chlorophenol instead of 3-chlorophenol. Dimethyl [4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]phosphonate product was obtained as a light yellow oil (90%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86-7.95 (m, 2H), 7.84-7.82 (m, 2H), 7.43-7.50 (m, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 1.34 (s, 12 H) ppm; MS [M+H] 312, [2M+H] 625.

[00431] Example 127. (4'-{(2S,3R)-3-[(3S)-3-(4-Fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid



prepared in analogous manner to Example 61 using dimethyl [4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]phosphonate (Example 126) in the reaction scheme instead of dimethyl [3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]phosphonate (Example 60). Final purification by reverse-phase HPLC (Polaris C18-A 10μ 250 x 21.2 mm column, 30% to 59% acetonitrile-0.1% trifluoroacetic acid in water) afforded (4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid as a white powder (62%); ^{1}H NMR (300 MHz, CD_3OD) δ7.8 (dd, J = 8.0, 13.0 Hz, 1H), 7.68 (dd, J = 3.2, 8.0 Hz, 1H), 6.9-7.4 (m, 14H), 5.17 (d, J = 2.1 Hz, 1H), 4.60-4.66 (m, 1H), 3.13-3.22 (m, 1H), 1.8-2.1 (m, 4H) ppm; MS [M-H] 546, [2M-H] 1093.

[00432] Example 128. Sodium 4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-sulfonate



5-Bromo-2-{(2S,3R)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-oxo-1-phenylazetidin-2-yl}phenyl acetate (850 mg, 1.36

mmol) and 4-thioanisoleboronic acid (252 mg, 1.50 mmol) were dissolved in dioxane (13.6 mL). Cesium carbonate (882 mg, 2.71 mmol) and solid bis(1-adamantylamine)palladium(0) (113 mg, 0.21 mmol) were added and the vessel was vacuum/nitrogen purged (3x). The reaction was stirred vigorously for 4 h at 80 °C under a nitrogen atmosphere and then cooled and reacted with acetic anhydride (0.70 mL, 7.3 mmol) and 4-dimethylamino-pyridine (185.6 mg, 1.52 mmol). After 15 min, the mixture was poured into 1.0 N hydrochloric acid (60 mL), extracted with 1:1 ethyl acetate-hexane (60 mL), washed with brine (60 mL), dried over sodium sulfate, filtered, concentrated and purified by chromatography (40 g silica gel, 5% to 50% ethyl acetate-hexane) to afford 4-{(2S,3R)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-oxo-1-phenylazetidin-2-yl}-4'-(methylthio)biphenyl-3-yl acetate (478 mg, 52% yield) as a white foam; R_f 0.41 (1:4 ethyl acetate-hexane).

[00433] 4-{(2S,3R)-3-[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)propyl]-4-oxo-1-phenylazetidin-2-yl}-4'-(methylthio)biphenyl-3-yl acetate (478 mg, 0.713 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0°C. 3-Chlorobenzenecarbo-peroxoic acid (134.5 mg, 0.779 mmol) was added in portions while monitoring by TLC and LCMS to make the arylsulfoxide. Once addition was complete the reaction was poured into quarter saturated sodium bicarbonate solution (60 mL), extracted with dichloromethane (60 mL) and ethyl acetate (60 mL), the combined organic layers were dried over sodium sulfate, filtered and concentrated with toluene. The residue was dissolved in dichloromethane (10 mL) and the Pummerer rearrangement was effected by the addition of trifluoroacetic anhydride (250 µL, 372 mg, 1.77 mmol). The reaction was stirred at room temperature for 8.5 h and then concentrated with toluene and diluted with a solution of degassed methanol (3.0 mL), triethylamine (3.0 mL) and water (1.0 mL). After 2.75 h the golden yellow solution was concentrated, transferred into a polypropylene Falcon® tube with acetonitrile (10.0 mL) and diluted with 48% hydrofluoric acid (1.0 mL). The reaction was stirred for 4 h at room temperature and then poured into 0.5 M potassium phosphate (50 mL), extracted with ethyl acetate (60 mL), washed with water (60 mL) and brine (60 mL), dried over sodium sulfate, filtered, concentrated and purified by chromatography (40 g silica gel, 10% to 100% ethyl acetate-hexane) to

afford a mixture of compounds (some impurities and oxidized desired material). The residue was used as is in the next step.

[00434] The residue was dissolved in dichloromethane (10 mL) and added drop-wise to a solution of 3-chlorobenzenecarboperoxoic acid (489 mg, 2.83 mmol) in dichloromethane (10 mL). Dichloromethane (5 mL) was used to help transfer the material and the mixture was stirred at room temperature for 15 min. The reaction was quenched by addition of triethylamine (4 mL), concentrated, dissolved in methanol, filtered through a 0.45 μ Whatman® filter, concentrated again, purified by reverse-phase HPLC (Polaris C18-A 10μ 250 x 21.2 mm column, 5% to 100% acetonitrile-0.1% triethylamine in water) and treated with Dowex® sodium ion exchange resin to afford sodium 4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-sulfonate (249.0 mg, 57% yield) as a light pale purple solid; ^{1}H NMR (300 MHz, CD_3OD) δ 7.88 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H), 7.35-7.19 (m, 7H), 7.14-7.11 (m, 2H), 7.03-6.97 (m, 3H), 5.14 (d, J = 2.2 Hz, 1H), 4.63-4.59 (m, 1H), 3.17-3.08 (m, 1H), 2.04-1.87 (m, 4H) ppm; MS [M-Na] 546.0.

[00435] The following examples 129 and 130 were also prepared according to methods decribed above:

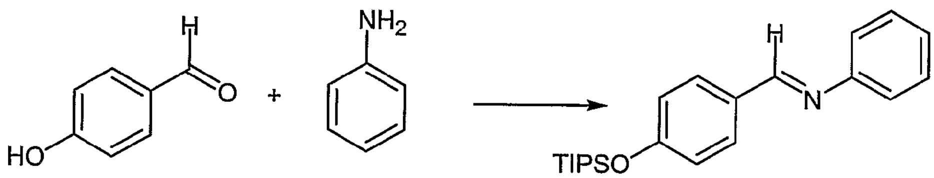
[00436] Example 129. (3R,4S)-4-(4'-fluorobiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one

[00437] Example 130. -(3R,4S)-4-(2',5'-difluorobiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one

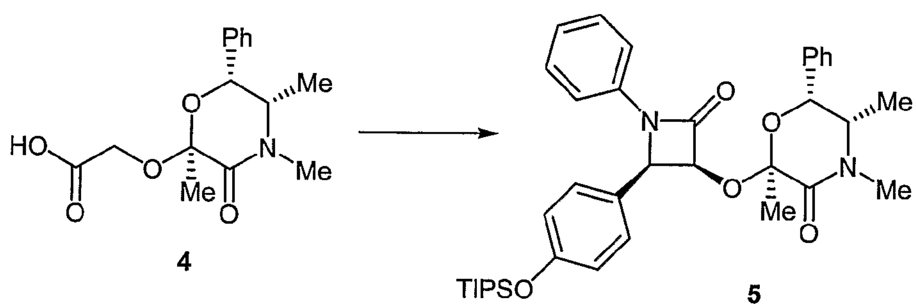
[00438] Example 131. (4R,5R)-5-((S)-3-(4-fluorophenyl)-3-hydroxypropyl)-4-(4-hydroxyphenyl)-3-phenyloxazolidine-2-thione (**10**)

[00439] The preparation of analogue **10** starts by the condensation of commercially available 4-hydroxybenzaldehyde (**1**) with aniline (**2**) to produce the corresponding imine. Protection of the hydroxyl moiety of the imine was accomplished by treatment with triisopropylsilyl chloride in the presence of imidazole in DMF to provide **3**. Treatment of **4** (prepared according to the method of B. A. Shinkre, V. G. Puranik, B, M. Bhawal, A. Deshmukh, *Tetrahedron Asymmetry* **2003**, *14*, 453) with triphosgene [$(Cl_3CO)_2CO$] and triethylamine in the presence of **3** provides the beta-lactam **5**. A

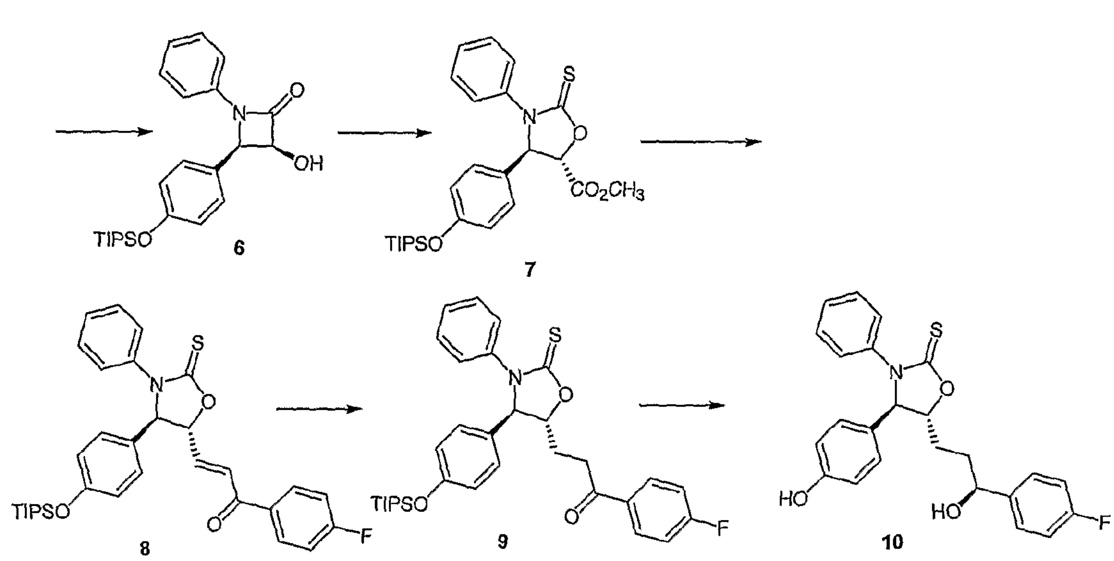
solution of ketal **5** is dissolved in tetrahydrofuran and water with a catalytic amount of *para*-toluenesulfonic acid to promote hydrolysis to alcohol **6**. Alcohol **6** is then treated with sodium methoxide in methanol to effect conversion to the methyl ester *via beta*-lactam ring opening. Reaction of the resulting alcohol with thiophosgene in the presence of diisopropylethylamine and *N,N*-dimethylaminopyridine (DMAP) gives the 1,3-oxazolidine-2-thione **7**. The ester moiety of **7** is then converted into the corresponding hydroxymethyl substituent upon treatment with sodium cyanoborohydride. Swern oxidation converts the hydroxymethyl substituent into the corresponding aldehyde which is then reacted with the Wittig reagent 1-(4-fluorophenyl)-2-triphenyl-λ^5-phosphanylidene)-ethanone to give the ketone **8**. Catalytic hydrogenation of **8** over palladium on carbon reduces the double bond to give ketone **9** which is reduced with borane dimethylsulfide complex in the presence of a catalytic amount of tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-c][1,3,2]oxazaborole, (R-CBS), followed by treatment with pyridine HF complex to give the desired compound **10**.



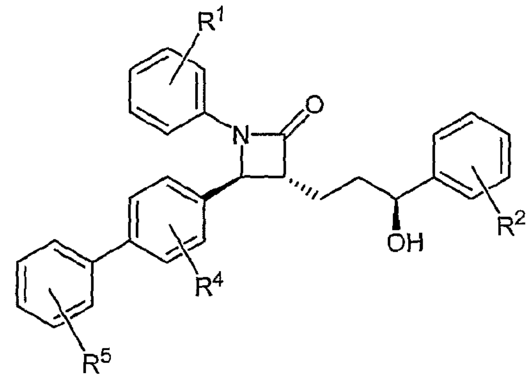
1 2 3



4 5



[00440] Also within the invention are compounds described by Table 3, together with Table 4 and Formula VIII which is shown below.

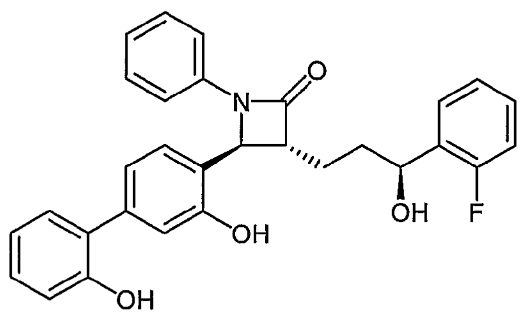


VIII

[00441] In these embodiments, R^1 and R^2 are independently chosen from H, F, CN, Cl, CH_3, OCH_3, OCF_3, OCF_2H, CF_3, CF_2H, and CH_2F; R^4 is chosen from H, Cl, F, CH_3, OCH_3, OH, $B(OH)_2$, and SH; R^5 is chosen from OH, SO_3H, PO_3H_2, CH_2OH, COOH, CHO, D-glucitol, a C-glysosyl compound and a sugar and only one R substitution is allowed on any aromatic ring. For example, where R^5 is –OH, all of the other substituents on the corresponding aromatic ring are H. Of course, where a given R group is H (e.g., R^1) all of the substituents on the corresponding aromatic ring are also H. In Table 4 when the R^4 substituent position is defined as 3-, the substitution occurs at the position ortho to the azetidinone ring. In Table 4 when the

R^4 substituent position is defined as 2-, the substitution occurs at the position meta to the azetidinone ring.

[00442] Each row in Table 3 defines a unique subset of R group substituents which can be systematically substituted in an iterative fashion into Formula VIII at the positions specified by each row of Table 4 to generate specific compounds within Formula VIII. For example, in Table 3, row 1, R^1 is H, R^2 is F, R^4 is OH, and R^5 is OH. Substituting this set of R groups into Formula VIII according to the placement defined by row 1 of Table 4 (i.e., R^1 is ortho, R^2 is ortho, R^4 is 3- and R^5 is ortho) yields



(3R,4S)-4-(2',3-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one.

[00443] Similarly, (3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one is disclosed by the using values in Table 3, row 1 to substitute Formula VIII according to Table 4, row 2.

[00444] Tables 5-20 comprise the compounds disclosed by substituting the substituents listed in Table 3 rows 1-16 into Formula VIII according to the placement defined by each row in Table 4. It should be understood that the compounds listed in Tables 5-20 are only a small subset of the compounds described by the systematic iterative substitution of the substituents in each row of Table 3 into generic Formula VIII according to the placement defined by each row of Table 4.

Table 3

Row	R1	R2	R4	R5
1	H	F	OH	OH
2	H	F	OH	D-glucitol
3	H	F	OH	SO_3H

4	H	F	OH	PO_3H_2
5	H	H	OH	OH
6	H	H	OH	D-glucitol
7	H	H	OH	SO_3H
8	H	H	OH	PO_3H_2
9	H	Cl	OH	OH
10	H	Cl	OH	D-glucitol
11	H	Cl	OH	SO_3H
12	H	Cl	OH	PO_3H_2
13	F	H	OH	OH
14	F	H	OH	D-glucitol
15	F	H	OH	SO_3H
16	F	H	OH	PO_3H_2
17	F	F	OH	OH
18	F	F	OH	D-glucitol
19	F	F	OH	SO_3H
20	F	F	OH	PO_3H_2
21	F	Cl	OH	OH
22	F	Cl	OH	D-glucitol
23	F	Cl	OH	SO_3H
24	F	Cl	OH	PO_3H_2
25	Cl	H	OH	OH
26	Cl	H	OH	D-glucitol
27	Cl	H	OH	SO_3H
28	Cl	H	OH	PO_3H_2
29	Cl	F	OH	OH
30	Cl	F	OH	D-glucitol
31	Cl	F	OH	SO_3H
32	Cl	F	OH	PO_3H_2
33	Cl	Cl	OH	OH
34	Cl	Cl	OH	D-glucitol
35	Cl	Cl	OH	SO_3H
36	Cl	Cl	OH	PO_3H_2
37	H	H	H	OH
38	H	H	H	D-glucitol
39	H	H	H	SO_3H
40	H	H	H	PO_3H_2
41	H	H	H	CHO

42	H	H	H	COOH
43	H	H	H	CH_2OH
44	H	H	H	sugar
45	H	H	H	C-glycosyl compound
46	H	H	OH	CHO
47	H	H	OH	COOH
48	H	H	OH	CH_2OH
49	H	H	OH	sugar
50	H	H	OH	C-glycosyl compound
51	H	H	CH_3	OH
52	H	H	CH_3	D-glucitol
53	H	H	CH_3	SO_3H
54	H	H	CH_3	PO_3H_2
55	H	H	CH_3	CHO
56	H	H	CH_3	COOH
57	H	H	CH_3	CH_2OH
58	H	H	CH_3	sugar
59	H	H	CH_3	C-glycosyl compound
60	H	H	Cl	OH
61	H	H	Cl	D-glucitol
62	H	H	Cl	SO_3H
63	H	H	Cl	PO_3H_2
64	H	H	Cl	CHO
65	H	H	Cl	COOH
66	H	H	Cl	CH_2OH
67	H	H	Cl	sugar
68	H	H	Cl	C-glycosyl compound
69	H	H	$B(OH)_2$	OH
70	H	H	$B(OH)_2$	D-glucitol
71	H	H	$B(OH)_2$	SO_3H
72	H	H	$B(OH)_2$	PO_3H_2
73	H	H	$B(OH)_2$	CHO
74	H	H	$B(OH)_2$	COOH
75	H	H	$B(OH)_2$	CH_2OH
76	H	H	$B(OH)_2$	sugar
77	H	H	$B(OH)_2$	C-glycosyl compound
78	H	H	SH	OH

79	H	H	SH	D-glucitol
80	H	H	SH	SO_3H
81	H	H	SH	PO_3H_2
82	H	H	SH	CHO
83	H	H	SH	COOH
84	H	H	SH	CH_2OH
85	H	H	SH	sugar
86	H	H	SH	C-glycosyl compound
87	H	H	OCH_3	OH
88	H	H	OCH_3	D-glucitol
89	H	H	OCH_3	SO_3H
90	H	H	OCH_3	PO_3H_2
91	H	H	OCH_3	CHO
92	H	H	OCH_3	COOH
93	H	H	OCH_3	CH_2OH
94	H	H	OCH_3	sugar
95	H	H	OCH_3	C-glycosyl compound
96	H	F	H	OH
97	H	F	H	D-glucitol
98	H	F	H	SO_3H
99	H	F	H	PO_3H_2
100	H	F	H	CHO
101	H	F	H	COOH
102	H	F	H	CH_2OH
103	H	F	H	sugar
104	H	F	H	C-glycosyl compound
105	H	F	OH	CHO
106	H	F	OH	COOH
107	H	F	OH	CH_2OH
108	H	F	OH	sugar
109	H	F	OH	C-glycosyl compound
110	H	F	CH_3	OH
111	H	F	CH_3	D-glucitol
112	H	F	CH_3	SO_3H
113	H	F	CH_3	PO_3H_2
114	H	F	CH_3	CHO
115	H	F	CH_3	COOH

116	H	F	CH_3	CH_2OH
117	H	F	CH_3	sugar
118	H	F	CH_3	C-glycosyl compound
119	H	F	Cl	OH
120	H	F	Cl	D-glucitol
121	H	F	Cl	SO_3H
122	H	F	Cl	PO_3H_2
123	H	F	Cl	CHO
124	H	F	Cl	COOH
125	H	F	Cl	CH_2OH
126	H	F	Cl	sugar
127	H	F	Cl	C-glycosyl compound
128	H	F	$B(OH)_2$	OH
129	H	F	$B(OH)_2$	D-glucitol
130	H	F	$B(OH)_2$	SO_3H
131	H	F	$B(OH)_2$	PO_3H_2
132	H	F	$B(OH)_2$	CHO
133	H	F	$B(OH)_2$	COOH
134	H	F	$B(OH)_2$	CH_2OH
135	H	F	$B(OH)_2$	sugar
136	H	F	$B(OH)_2$	C-glycosyl compound
137	H	F	SH	OH
138	H	F	SH	D-glucitol
139	H	F	SH	SO_3H
140	H	F	SH	PO_3H_2
141	H	F	SH	CHO
142	H	F	SH	COOH
143	H	F	SH	CH_2OH
144	H	F	SH	sugar
145	H	F	SH	C-glycosyl compound
146	H	F	OCH_3	OH
147	H	F	OCH_3	D-glucitol
148	H	F	OCH_3	SO_3H
149	H	F	OCH_3	PO_3H_2
150	H	F	OCH_3	CHO
151	H	F	OCH_3	COOH
152	H	F	OCH_3	CH_2OH

153	H	F	OCH_3	sugar
154	H	F	OCH_3	C-glycosyl compound
155	H	Cl	H	OH
156	H	Cl	H	D-glucitol
157	H	Cl	H	SO_3H
158	H	Cl	H	PO_3H_2
159	H	Cl	H	CHO
160	H	Cl	H	COOH
161	H	Cl	H	CH_2OH
162	H	Cl	H	sugar
163	H	Cl	H	C-glycosyl compound
164	H	Cl	OH	CHO
165	H	Cl	OH	COOH
166	H	Cl	OH	CH_2OH
167	H	Cl	OH	sugar
168	H	Cl	OH	C-glycosyl compound
169	H	Cl	CH_3	OH
170	H	Cl	CH_3	D-glucitol
171	H	Cl	CH_3	SO_3H
172	H	Cl	CH_3	PO_3H_2
173	H	Cl	CH_3	CHO
174	H	Cl	CH_3	COOH
175	H	Cl	CH_3	CH_2OH
176	H	Cl	CH_3	sugar
177	H	Cl	CH_3	C-glycosyl compound
178	H	Cl	Cl	OH
179	H	Cl	Cl	D-glucitol
180	H	Cl	Cl	SO_3H
181	H	Cl	Cl	PO_3H_2
182	H	Cl	Cl	CHO
183	H	Cl	Cl	COOH
184	H	Cl	Cl	CH_2OH
185	H	Cl	Cl	sugar
186	H	Cl	Cl	C-glycosyl compound
187	H	Cl	$B(OH)_2$	OH
188	H	Cl	$B(OH)_2$	D-glucitol
189	H	Cl	$B(OH)_2$	SO_3H
190	H	Cl	$B(OH)_2$	PO_3H_2

191	H	Cl	$B(OH)_2$	CHO
192	H	Cl	$B(OH)_2$	COOH
193	H	Cl	$B(OH)_2$	CH_2OH
194	H	Cl	$B(OH)_2$	sugar
195	H	Cl	$B(OH)_2$	C-glycosyl compound
196	H	Cl	SH	OH
197	H	Cl	SH	D-glucitol
198	H	Cl	SH	SO_3H
199	H	Cl	SH	PO_3H_2
200	H	Cl	SH	CHO
201	H	Cl	SH	COOH
202	H	Cl	SH	CH_2OH
203	H	Cl	SH	sugar
204	H	Cl	SH	C-glycosyl compound
205	H	Cl	OCH_3	OH
206	H	Cl	OCH_3	D-glucitol
207	H	Cl	OCH_3	SO_3H
208	H	Cl	OCH_3	PO_3H_2
209	H	Cl	OCH_3	CHO
210	H	Cl	OCH_3	COOH
211	H	Cl	OCH_3	CH_2OH
212	H	Cl	OCH_3	sugar
213	H	Cl	OCH_3	C-glycosyl compound
214	H	CN	H	OH
215	H	CN	H	D-glucitol
216	H	CN	H	SO_3H
217	H	CN	H	PO_3H_2
218	H	CN	H	CHO
219	H	CN	H	COOH
220	H	CN	H	CH_2OH
221	H	CN	H	sugar
222	H	CN	H	C-glycosyl compound
223	H	CN	OH	OH
224	H	CN	OH	D-glucitol
225	H	CN	OH	SO_3H
226	H	CN	OH	PO_3H_2
227	H	CN	OH	CHO
228	H	CN	OH	COOH

229	H	CN	OH	CH_2OH
230	H	CN	OH	sugar
231	H	CN	OH	C-glycosyl compound
232	H	CN	CH_3	OH
233	H	CN	CH_3	D-glucitol
234	H	CN	CH_3	SO_3H
235	H	CN	CH_3	PO_3H_2
236	H	CN	CH_3	CHO
237	H	CN	CH_3	COOH
238	H	CN	CH_3	CH_2OH
239	H	CN	CH_3	sugar
240	H	CN	CH_3	C-glycosyl compound
241	H	CN	Cl	OH
242	H	CN	Cl	D-glucitol
243	H	CN	Cl	SO_3H
244	H	CN	Cl	PO_3H_2
245	H	CN	Cl	CHO
246	H	CN	Cl	COOH
247	H	CN	Cl	CH_2OH
248	H	CN	Cl	sugar
249	H	CN	Cl	C-glycosyl compound
250	H	CN	$B(OH)_2$	OH
251	H	CN	$B(OH)_2$	D-glucitol
252	H	CN	$B(OH)_2$	SO_3H
253	H	CN	$B(OH)_2$	PO_3H_2
254	H	CN	$B(OH)_2$	CHO
255	H	CN	$B(OH)_2$	COOH
256	H	CN	$B(OH)_2$	CH_2OH
257	H	CN	$B(OH)_2$	sugar
258	H	CN	$B(OH)_2$	C-glycosyl compound
259	H	CN	SH	OH
260	H	CN	SH	D-glucitol
261	H	CN	SH	SO_3H
262	H	CN	SH	PO_3H_2
263	H	CN	SH	CHO
264	H	CN	SH	COOH
265	H	CN	SH	CH_2OH

266	H	CN	SH	sugar
267	H	CN	SH	C-glycosyl compound
268	H	CN	OCH_3	OH
269	H	CN	OCH_3	D-glucitol
270	H	CN	OCH_3	SO_3H
271	H	CN	OCH_3	PO_3H_2
272	H	CN	OCH_3	CHO
273	H	CN	OCH_3	COOH
274	H	CN	OCH_3	CH_2OH
275	H	CN	OCH_3	sugar
276	H	CN	OCH_3	C-glycosyl compound
277	H	CH_3[a]	H	OH
278	H	CH_3[a]	H	D-glucitol
279	H	CH_3[a]	H	SO_3H
280	H	CH_3[a]	H	PO_3H_2
281	H	CH_3[a]	H	CHO
282	H	CH_3[a]	H	COOH
283	H	CH_3[a]	H	CH_2OH
284	H	CH_3[a]	H	sugar
285	H	CH_3[a]	H	C-glycosyl compound
286	H	CH_3[a]	OH	OH
287	H	CH_3[a]	OH	D-glucitol
288	H	CH_3[a]	OH	SO_3H
289	H	CH_3[a]	OH	PO_3H_2
290	H	CH_3[a]	OH	CHO
291	H	CH_3[a]	OH	COOH
292	H	CH_3[a]	OH	CH_2OH
293	H	CH_3[a]	OH	sugar
294	H	CH_3[a]	OH	C-glycosyl compound
295	H	CH_3[a]	CH_3	OH
296	H	CH_3[a]	CH_3	D-glucitol
297	H	CH_3[a]	CH_3	SO_3H
298	H	CH_3[a]	CH_3	PO_3H_2
299	H	CH_3[a]	CH_3	CHO

300	H	CH_3[a]	CH_3	COOH
301	H	CH_3[a]	CH_3	CH_2OH
302	H	CH_3[a]	CH_3	sugar
303	H	CH_3[a]	CH_3	C-glycosyl compound
304	H	CH_3[a]	Cl	OH
305	H	CH_3[a]	Cl	D-glucitol
306	H	CH_3[a]	Cl	SO_3H
307	H	CH_3[a]	Cl	PO_3H_2
308	H	CH_3[a]	Cl	CHO
309	H	CH_3[a]	Cl	COOH
310	H	CH_3[a]	Cl	CH_2OH
311	H	CH_3[a]	Cl	sugar
312	H	CH_3[a]	Cl	C-glycosyl compound
313	H	CH_3[a]	$B(OH)_2$	OH
314	H	CH_3[a]	$B(OH)_2$	D-glucitol
315	H	CH_3[a]	$B(OH)_2$	SO_3H
316	H	CH_3[a]	$B(OH)_2$	PO_3H_2
317	H	CH_3[a]	$B(OH)_2$	CHO
318	H	CH_3[a]	$B(OH)_2$	COOH
319	H	CH_3[a]	$B(OH)_2$	CH_2OH
320	H	CH_3[a]	$B(OH)_2$	sugar
321	H	CH_3[a]	$B(OH)_2$	C-glycosyl compound
322	H	CH_3[a]	SH	OH
323	H	CH_3[a]	SH	D-glucitol
324	H	CH_3[a]	SH	SO_3H
325	H	CH_3[a]	SH	PO_3H_2
326	H	CH_3[a]	SH	CHO
327	H	CH_3[a]	SH	COOH
328	H	CH_3[a]	SH	CH_2OH
329	H	CH_3[a]	SH	sugar
330	H	CH_3[a]	SH	C-glycosyl compound
331	H	CH_3[a]	OCH_3	OH
332	H	CH_3[a]	OCH_3	D-glucitol

333	H	CH_3[a]	OCH_3	SO_3H
334	H	CH_3[a]	OCH_3	PO_3H_2
335	H	CH_3[a]	OCH_3	CHO
336	H	CH_3[a]	OCH_3	COOH
337	H	CH_3[a]	OCH_3	CH_2OH
338	H	CH_3[a]	OCH_3	sugar
339	H	CH_3[a]	OCH_3	C-glycosyl compound
340	H	OCH_3[b]	H	OH
341	H	OCH_3[b]	H	D-glucitol
342	H	OCH_3[b]	H	SO_3H
343	H	OCH_3[b]	H	PO_3H_2
344	H	OCH_3[b]	H	CHO
345	H	OCH_3[b]	H	COOH
346	H	OCH_3[b]	H	CH_2OH
347	H	OCH_3[b]	H	sugar
348	H	OCH_3[b]	H	C-glycosyl compound
349	H	OCH_3[b]	OH	OH
350	H	OCH_3[b]	OH	D-glucitol
351	H	OCH_3[b]	OH	SO_3H
352	H	OCH_3[b]	OH	PO_3H_2
353	H	OCH_3[b]	OH	CHO
354	H	OCH_3[b]	OH	COOH
355	H	OCH_3[b]	OH	CH_2OH
356	H	OCH_3[b]	OH	sugar
357	H	OCH_3[b]	OH	C-glycosyl compound
358	H	OCH_3[b]	CH_3	OH
359	H	OCH_3[b]	CH_3	D-glucitol
360	H	OCH_3[b]	CH_3	SO_3H
361	H	OCH_3[b]	CH_3	PO_3H_2
362	H	OCH_3[b]	CH_3	CHO
363	H	OCH_3[b]	CH_3	COOH
364	H	OCH_3[b]	CH_3	CH_2OH
365	H	OCH_3[b]	CH_3	sugar

366	H	OCH_3[b]	CH_3	C-glycosyl compound
367	H	OCH_3[b]	Cl	OH
368	H	OCH_3[b]	Cl	D-glucitol
369	H	OCH_3[b]	Cl	SO_3H
370	H	OCH_3[b]	Cl	PO_3H_2
371	H	OCH_3[b]	Cl	CHO
372	H	OCH_3[b]	Cl	COOH
373	H	OCH_3[b]	Cl	CH_2OH
374	H	OCH_3[b]	Cl	sugar
375	H	OCH_3[b]	Cl	C-glycosyl compound
376	H	OCH_3[b]	$B(OH)_2$	OH
377	H	OCH_3[b]	$B(OH)_2$	D-glucitol
378	H	OCH_3[b]	$B(OH)_2$	SO_3H
379	H	OCH_3[b]	$B(OH)_2$	PO_3H_2
380	H	OCH_3[b]	$B(OH)_2$	CHO
381	H	OCH_3[b]	$B(OH)_2$	COOH
382	H	OCH_3[b]	$B(OH)_2$	CH_2OH
383	H	OCH_3[b]	$B(OH)_2$	sugar
384	H	OCH_3[b]	$B(OH)_2$	C-glycosyl compound
385	H	OCH_3[b]	SH	OH
386	H	OCH_3[b]	SH	D-glucitol
387	H	OCH_3[b]	SH	SO_3H
388	H	OCH_3[b]	SH	PO_3H_2
389	H	OCH_3[b]	SH	CHO
390	H	OCH_3[b]	SH	COOH
391	H	OCH_3[b]	SH	CH_2OH
392	H	OCH_3[b]	SH	sugar
393	H	OCH_3[b]	SH	C-glycosyl compound
394	H	OCH_3[b]	OCH_3	OH
395	H	OCH_3[b]	OCH_3	D-glucitol
396	H	OCH_3[b]	OCH_3	SO_3H
397	H	OCH_3[b]	OCH_3	PO_3H_2
398	H	OCH_3[b]	OCH_3	CHO

399	H	OCH_3[b]	OCH_3	COOH
400	H	OCH_3[b]	OCH_3	CH_2OH
401	H	OCH_3[b]	OCH_3	sugar
402	H	OCH_3[b]	OCH_3	C-glycosyl compound
403	F	H	H	OH
404	F	H	H	D-glucitol
405	F	H	H	SO_3H
406	F	H	H	PO_3H_2
407	F	H	H	CHO
408	F	H	H	COOH
409	F	H	H	CH_2OH
410	F	H	H	sugar
411	F	H	H	C-glycosyl compound
412	F	H	OH	CHO
413	F	H	OH	COOH
414	F	H	OH	CH_2OH
415	F	H	OH	sugar
416	F	H	OH	C-glycosyl compound
417	F	H	CH_3	OH
418	F	H	CH_3	D-glucitol
419	F	H	CH_3	SO_3H
420	F	H	CH_3	PO_3H_2
421	F	H	CH_3	CHO
422	F	H	CH_3	COOH
423	F	H	CH_3	CH_2OH
424	F	H	CH_3	sugar
425	F	H	CH_3	C-glycosyl compound
426	F	H	Cl	OH
427	F	H	Cl	D-glucitol
428	F	H	Cl	SO_3H
429	F	H	Cl	PO_3H_2
430	F	H	Cl	CHO
431	F	H	Cl	COOH
432	F	H	Cl	CH_2OH
433	F	H	Cl	sugar
434	F	H	Cl	C-glycosyl compound
435	F	H	$B(OH)_2$	OH

436	F	H	$B(OH)_2$	D-glucitol
437	F	H	$B(OH)_2$	SO_3H
438	F	H	$B(OH)_2$	PO_3H_2
439	F	H	$B(OH)_2$	CHO
440	F	H	$B(OH)_2$	COOH
441	F	H	$B(OH)_2$	CH_2OH
442	F	H	$B(OH)_2$	sugar
443	F	H	$B(OH)_2$	C-glycosyl compound
444	F	H	SH	OH
445	F	H	SH	D-glucitol
446	F	H	SH	SO_3H
447	F	H	SH	PO_3H_2
448	F	H	SH	CHO
449	F	H	SH	COOH
450	F	H	SH	CH_2OH
451	F	H	SH	sugar
452	F	H	SH	C-glycosyl compound
453	F	H	OCH_3	OH
454	F	H	OCH_3	D-glucitol
455	F	H	OCH_3	SO_3H
456	F	H	OCH_3	PO_3H_2
457	F	H	OCH_3	CHO
458	F	H	OCH_3	COOH
459	F	H	OCH_3	CH_2OH
460	F	H	OCH_3	sugar
461	F	H	OCH_3	C-glycosyl compound
462	F	F	H	OH
463	F	F	H	D-glucitol
464	F	F	H	SO_3H
465	F	F	H	PO_3H_2
466	F	F	H	CHO
467	F	F	H	COOH
468	F	F	H	CH_2OH
469	F	F	H	sugar
470	F	F	H	C-glycosyl compound
471	F	F	OH	CHO
472	F	F	OH	COOH

473	F	F	OH	CH_2OH
474	F	F	OH	sugar
475	F	F	OH	C-glycosyl compound
476	F	F	CH_3	OH
477	F	F	CH_3	D-glucitol
478	F	F	CH_3	SO_3H
479	F	F	CH_3	PO_3H_2
480	F	F	CH_3	CHO
481	F	F	CH_3	COOH
482	F	F	CH_3	CH_2OH
483	F	F	CH_3	sugar
484	F	F	CH_3	C-glycosyl compound
485	F	F	Cl	OH
486	F	F	Cl	D-glucitol
487	F	F	Cl	SO_3H
488	F	F	Cl	PO_3H_2
489	F	F	Cl	CHO
490	F	F	Cl	COOH
491	F	F	Cl	CH_2OH
492	F	F	Cl	sugar
493	F	F	Cl	C-glycosyl compound
494	F	F	$B(OH)_2$	OH
495	F	F	$B(OH)_2$	D-glucitol
496	F	F	$B(OH)_2$	SO_3H
497	F	F	$B(OH)_2$	PO_3H_2
498	F	F	$B(OH)_2$	CHO
499	F	F	$B(OH)_2$	COOH
500	F	F	$B(OH)_2$	CH_2OH
501	F	F	$B(OH)_2$	sugar
502	F	F	$B(OH)_2$	C-glycosyl compound
503	F	F	SH	OH
504	F	F	SH	D-glucitol
505	F	F	SH	SO_3H
506	F	F	SH	PO_3H_2
507	F	F	SH	CHO
508	F	F	SH	COOH
509	F	F	SH	CH_2OH

510	F	F	SH	sugar
511	F	F	SH	C-glycosyl compound
512	F	F	OCH_3	OH
513	F	F	OCH_3	D-glucitol
514	F	F	OCH_3	SO_3H
515	F	F	OCH_3	PO_3H_2
516	F	F	OCH_3	CHO
517	F	F	OCH_3	COOH
518	F	F	OCH_3	CH_2OH
519	F	F	OCH_3	sugar
520	F	F	OCH_3	C-glycosyl compound
521	F	Cl	H	OH
522	F	Cl	H	D-glucitol
523	F	Cl	H	SO_3H
524	F	Cl	H	PO_3H_2
525	F	Cl	H	CHO
526	F	Cl	H	COOH
527	F	Cl	H	CH_2OH
528	F	Cl	H	sugar
529	F	Cl	H	C-glycosyl compound
530	F	Cl	OH	CHO
531	F	Cl	OH	COOH
532	F	Cl	OH	CH_2OH
533	F	Cl	OH	sugar
534	F	Cl	OH	C-glycosyl compound
535	F	Cl	CH_3	OH
536	F	Cl	CH_3	D-glucitol
537	F	Cl	CH_3	SO_3H
538	F	Cl	CH_3	PO_3H_2
539	F	Cl	CH_3	CHO
540	F	Cl	CH_3	COOH
541	F	Cl	CH_3	CH_2OH
542	F	Cl	CH_3	sugar
543	F	Cl	CH_3	C-glycosyl compound
544	F	Cl	Cl	OH
545	F	Cl	Cl	D-glucitol
546	F	Cl	Cl	SO_3H

547	F	Cl	Cl	PO_3H_2
548	F	Cl	Cl	CHO
549	F	Cl	Cl	COOH
550	F	Cl	Cl	CH_2OH
551	F	Cl	Cl	sugar
552	F	Cl	Cl	C-glycosyl compound
553	F	Cl	$B(OH)_2$	OH
554	F	Cl	$B(OH)_2$	D-glucitol
555	F	Cl	$B(OH)_2$	SO_3H
556	F	Cl	$B(OH)_2$	PO_3H_2
557	F	Cl	$B(OH)_2$	CHO
558	F	Cl	$B(OH)_2$	COOH
559	F	Cl	$B(OH)_2$	CH_2OH
560	F	Cl	$B(OH)_2$	sugar
561	F	Cl	$B(OH)_2$	C-glycosyl compound
562	F	Cl	SH	OH
563	F	Cl	SH	D-glucitol
564	F	Cl	SH	SO_3H
565	F	Cl	SH	PO_3H_2
566	F	Cl	SH	CHO
567	F	Cl	SH	COOH
568	F	Cl	SH	CH_2OH
569	F	Cl	SH	sugar
570	F	Cl	SH	C-glycosyl compound
571	F	Cl	OCH_3	OH
572	F	Cl	OCH_3	D-glucitol
573	F	Cl	OCH_3	SO_3H
574	F	Cl	OCH_3	PO_3H_2
575	F	Cl	OCH_3	CHO
576	F	Cl	OCH_3	COOH
577	F	Cl	OCH_3	CH_2OH
578	F	Cl	OCH_3	sugar
579	F	Cl	OCH_3	C-glycosyl compound
580	F	CN	H	OH
581	F	CN	H	D-glucitol
582	F	CN	H	SO_3H
583	F	CN	H	PO_3H_2

584	F	CN	H	CHO
585	F	CN	H	COOH
586	F	CN	H	CH_2OH
587	F	CN	H	sugar
588	F	CN	H	C-glycosyl compound
589	F	CN	OH	OH
590	F	CN	OH	D-glucitol
591	F	CN	OH	SO_3H
592	F	CN	OH	PO_3H_2
593	F	CN	OH	CHO
594	F	CN	OH	COOH
595	F	CN	OH	CH_2OH
596	F	CN	OH	sugar
597	F	CN	OH	C-glycosyl compound
598	F	CN	CH_3	OH
599	F	CN	CH_3	D-glucitol
600	F	CN	CH_3	SO_3H
601	F	CN	CH_3	PO_3H_2
602	F	CN	CH_3	CHO
603	F	CN	CH_3	COOH
604	F	CN	CH_3	CH_2OH
605	F	CN	CH_3	sugar
606	F	CN	CH_3	C-glycosyl compound
607	F	CN	Cl	OH
608	F	CN	Cl	D-glucitol
609	F	CN	Cl	SO_3H
610	F	CN	Cl	PO_3H_2
611	F	CN	Cl	CHO
612	F	CN	Cl	COOH
613	F	CN	Cl	CH_2OH
614	F	CN	Cl	sugar
615	F	CN	Cl	C-glycosyl compound
616	F	CN	$B(OH)_2$	OH
617	F	CN	$B(OH)_2$	D-glucitol
618	F	CN	$B(OH)_2$	SO_3H
619	F	CN	$B(OH)_2$	PO_3H_2
620	F	CN	$B(OH)_2$	CHO
621	F	CN	$B(OH)_2$	COOH

622	F	CN	$B(OH)_2$	CH_2OH
623	F	CN	$B(OH)_2$	sugar
624	F	CN	$B(OH)_2$	C-glycosyl compound
625	F	CN	SH	OH
626	F	CN	SH	D-glucitol
627	F	CN	SH	SO_3H
628	F	CN	SH	PO_3H_2
629	F	CN	SH	CHO
630	F	CN	SH	COOH
631	F	CN	SH	CH_2OH
632	F	CN	SH	sugar
633	F	CN	SH	C-glycosyl compound
634	F	CN	OCH_3	OH
635	F	CN	OCH_3	D-glucitol
636	F	CN	OCH_3	SO_3H
637	F	CN	OCH_3	PO_3H_2
638	F	CN	OCH_3	CHO
639	F	CN	OCH_3	COOH
640	F	CN	OCH_3	CH_2OH
641	F	CN	OCH_3	sugar
642	F	CN	OCH_3	C-glycosyl compound
643	F	CH_3[a]	H	OH
644	F	CH_3[a]	H	D-glucitol
645	F	CH_3[a]	H	SO_3H
646	F	CH_3[a]	H	PO_3H_2
647	F	CH_3[a]	H	CHO
648	F	CH_3[a]	H	COOH
649	F	CH_3[a]	H	CH_2OH
650	F	CH_3[a]	H	sugar
651	F	CH_3[a]	H	C-glycosyl compound
652	F	CH_3[a]	OH	OH
653	F	CH_3[a]	OH	D-glucitol
654	F	CH_3[a]	OH	SO_3H
655	F	CH_3[a]	OH	PO_3H_2
656	F	CH_3[a]	OH	CHO

657	F	CH_3[a]	OH	COOH
658	F	CH_3[a]	OH	CH_2OH
659	F	CH_3[a]	OH	sugar
660	F	CH_3[a]	OH	C-glycosyl compound
661	F	CH_3[a]	CH_3	OH
662	F	CH_3[a]	CH_3	D-glucitol
663	F	CH_3[a]	CH_3	SO_3H
664	F	CH_3[a]	CH_3	PO_3H_2
665	F	CH_3[a]	CH_3	CHO
666	F	CH_3[a]	CH_3	COOH
667	F	CH_3[a]	CH_3	CH_2OH
668	F	CH_3[a]	CH_3	sugar
669	F	CH_3[a]	CH_3	C-glycosyl compound
670	F	CH_3[a]	Cl	OH
671	F	CH_3[a]	Cl	D-glucitol
672	F	CH_3[a]	Cl	SO_3H
673	F	CH_3[a]	Cl	PO_3H_2
674	F	CH_3[a]	Cl	CHO
675	F	CH_3[a]	Cl	COOH
676	F	CH_3[a]	Cl	CH_2OH
677	F	CH_3[a]	Cl	sugar
678	F	CH_3[a]	Cl	C-glycosyl compound
679	F	CH_3[a]	$B(OH)_2$	OH
680	F	CH_3[a]	$B(OH)_2$	D-glucitol
681	F	CH_3[a]	$B(OH)_2$	SO_3H
682	F	CH_3[a]	$B(OH)_2$	PO_3H_2
683	F	CH_3[a]	$B(OH)_2$	CHO
684	F	CH_3[a]	$B(OH)_2$	COOH
685	F	CH_3[a]	$B(OH)_2$	CH_2OH
686	F	CH_3[a]	$B(OH)_2$	sugar
687	F	CH_3[a]	$B(OH)_2$	C-glycosyl compound
688	F	CH_3[a]	SH	OH
689	F	CH_3[a]	SH	D-glucitol

690	F	CH_3[a]	SH	SO_3H
691	F	CH_3[a]	SH	PO_3H_2
692	F	CH_3[a]	SH	CHO
693	F	CH_3[a]	SH	COOH
694	F	CH_3[a]	SH	CH_2OH
695	F	CH_3[a]	SH	sugar
696	F	CH_3[a]	SH	C-glycosyl compound
697	F	CH_3[a]	OCH_3	OH
698	F	CH_3[a]	OCH_3	D-glucitol
699	F	CH_3[a]	OCH_3	SO_3H
700	F	CH_3[a]	OCH_3	PO_3H_2
701	F	CH_3[a]	OCH_3	CHO
702	F	CH_3[a]	OCH_3	COOH
703	F	CH_3[a]	OCH_3	CH_2OH
704	F	CH_3[a]	OCH_3	sugar
705	F	CH_3[a]	OCH_3	C-glycosyl compound
706	F	OCH_3[b]	H	OH
707	F	OCH_3[b]	H	D-glucitol
708	F	OCH_3[b]	H	SO_3H
709	F	OCH_3[b]	H	PO_3H_2
710	F	OCH_3[b]	H	CHO
711	F	OCH_3[b]	H	COOH
712	F	OCH_3[b]	H	CH_2OH
713	F	OCH_3[b]	H	sugar
714	F	OCH_3[b]	H	C-glycosyl compound
715	F	OCH_3[b]	OH	OH
716	F	OCH_3[b]	OH	D-glucitol
717	F	OCH_3[b]	OH	SO_3H
718	F	OCH_3[b]	OH	PO_3H_2
719	F	OCH_3[b]	OH	CHO
720	F	OCH_3[b]	OH	COOH
721	F	OCH_3[b]	OH	CH_2OH
722	F	OCH_3[b]	OH	sugar

723	F	OCH_3[b]	OH	C-glycosyl compound
724	F	OCH_3[b]	CH_3	OH
725	F	OCH_3[b]	CH_3	D-glucitol
726	F	OCH_3[b]	CH_3	SO_3H
727	F	OCH_3[b]	CH_3	PO_3H_2
728	F	OCH_3[b]	CH_3	CHO
729	F	OCH_3[b]	CH_3	COOH
730	F	OCH_3[b]	CH_3	CH_2OH
731	F	OCH_3[b]	CH_3	sugar
732	F	OCH_3[b]	CH_3	C-glycosyl compound
733	F	OCH_3[b]	Cl	OH
734	F	OCH_3[b]	Cl	D-glucitol
735	F	OCH_3[b]	Cl	SO_3H
736	F	OCH_3[b]	Cl	PO_3H_2
737	F	OCH_3[b]	Cl	CHO
738	F	OCH_3[b]	Cl	COOH
739	F	OCH_3[b]	Cl	CH_2OH
740	F	OCH_3[b]	Cl	sugar
741	F	OCH_3[b]	Cl	C-glycosyl compound
742	F	OCH_3[b]	$B(OH)_2$	OH
743	F	OCH_3[b]	$B(OH)_2$	D-glucitol
744	F	OCH_3[b]	$B(OH)_2$	SO_3H
745	F	OCH_3[b]	$B(OH)_2$	PO_3H_2
746	F	OCH_3[b]	$B(OH)_2$	CHO
747	F	OCH_3[b]	$B(OH)_2$	COOH
748	F	OCH_3[b]	$B(OH)_2$	CH_2OH
749	F	OCH_3[b]	$B(OH)_2$	sugar
750	F	OCH_3[b]	$B(OH)_2$	C-glycosyl compound
751	F	OCH_3[b]	SH	OH
752	F	OCH_3[b]	SH	D-glucitol
753	F	OCH_3[b]	SH	SO_3H
754	F	OCH_3[b]	SH	PO_3H_2
755	F	OCH_3[b]	SH	CHO

756	F	OCH_3[b]	SH	COOH
757	F	OCH_3[b]	SH	CH_2OH
758	F	OCH_3[b]	SH	sugar
759	F	OCH_3[b]	SH	C-glycosyl compound
760	F	OCH_3[b]	OCH_3	OH
761	F	OCH_3[b]	OCH_3	D-glucitol
762	F	OCH_3[b]	OCH_3	SO_3H
763	F	OCH_3[b]	OCH_3	PO_3H_2
764	F	OCH_3[b]	OCH_3	CHO
765	F	OCH_3[b]	OCH_3	COOH
766	F	OCH_3[b]	OCH_3	CH_2OH
767	F	OCH_3[b]	OCH_3	sugar
768	F	OCH_3[b]	OCH_3	C-glycosyl compound
769	Cl	H	H	OH
770	Cl	H	H	D-glucitol
771	Cl	H	H	SO_3H
772	Cl	H	H	PO_3H_2
773	Cl	H	H	CHO
774	Cl	H	H	COOH
775	Cl	H	H	CH_2OH
776	Cl	H	H	sugar
777	Cl	H	H	C-glycosyl compound
778	Cl	H	OH	CHO
779	Cl	H	OH	COOH
780	Cl	H	OH	CH_2OH
781	Cl	H	OH	sugar
782	Cl	H	OH	C-glycosyl compound
783	Cl	H	CH_3	OH
784	Cl	H	CH_3	D-glucitol
785	Cl	H	CH_3	SO_3H
786	Cl	H	CH_3	PO_3H_2
787	Cl	H	CH_3	CHO
788	Cl	H	CH_3	COOH
789	Cl	H	CH_3	CH_2OH
790	Cl	H	CH_3	sugar
791	Cl	H	CH_3	C-glycosyl compound

792	Cl	H	Cl	OH
793	Cl	H	Cl	D-glucitol
794	Cl	H	Cl	SO_3H
795	Cl	H	Cl	PO_3H_2
796	Cl	H	Cl	CHO
797	Cl	H	Cl	COOH
798	Cl	H	Cl	CH_2OH
799	Cl	H	Cl	sugar
800	Cl	H	Cl	C-glycosyl compound
801	Cl	H	$B(OH)_2$	OH
802	Cl	H	$B(OH)_2$	D-glucitol
803	Cl	H	$B(OH)_2$	SO_3H
804	Cl	H	$B(OH)_2$	PO_3H_2
805	Cl	H	$B(OH)_2$	CHO
806	Cl	H	$B(OH)_2$	COOH
807	Cl	H	$B(OH)_2$	CH_2OH
808	Cl	H	$B(OH)_2$	sugar
809	Cl	H	$B(OH)_2$	C-glycosyl compound
810	Cl	H	SH	OH
811	Cl	H	SH	D-glucitol
812	Cl	H	SH	SO_3H
813	Cl	H	SH	PO_3H_2
814	Cl	H	SH	CHO
815	Cl	H	SH	COOH
816	Cl	H	SH	CH_2OH
817	Cl	H	SH	sugar
818	Cl	H	SH	C-glycosyl compound
819	Cl	H	OCH_3	OH
820	Cl	H	OCH_3	D-glucitol
821	Cl	H	OCH_3	SO_3H
822	Cl	H	OCH_3	PO_3H_2
823	Cl	H	OCH_3	CHO
824	Cl	H	OCH_3	COOH
825	Cl	H	OCH_3	CH_2OH
826	Cl	H	OCH_3	sugar
827	Cl	H	OCH_3	C-glycosyl compound
828	Cl	F	H	OH

829	Cl	F	H	D-glucitol
830	Cl	F	H	SO_3H
831	Cl	F	H	PO_3H_2
832	Cl	F	H	CHO
833	Cl	F	H	COOH
834	Cl	F	H	CH_2OH
835	Cl	F	H	sugar
836	Cl	F	H	C-glycosyl compound
837	Cl	F	OH	CHO
838	Cl	F	OH	COOH
839	Cl	F	OH	CH_2OH
840	Cl	F	OH	sugar
841	Cl	F	OH	C-glycosyl compound
842	Cl	F	CH_3	OH
843	Cl	F	CH_3	D-glucitol
844	Cl	F	CH_3	SO_3H
845	Cl	F	CH_3	PO_3H_2
846	Cl	F	CH_3	CHO
847	Cl	F	CH_3	COOH
848	Cl	F	CH_3	CH_2OH
849	Cl	F	CH_3	sugar
850	Cl	F	CH_3	C-glycosyl compound
851	Cl	F	Cl	OH
852	Cl	F	Cl	D-glucitol
853	Cl	F	Cl	SO_3H
854	Cl	F	Cl	PO_3H_2
855	Cl	F	Cl	CHO
856	Cl	F	Cl	COOH
857	Cl	F	Cl	CH_2OH
858	Cl	F	Cl	sugar
859	Cl	F	Cl	C-glycosyl compound
860	Cl	F	$B(OH)_2$	OH
861	Cl	F	$B(OH)_2$	D-glucitol
862	Cl	F	$B(OH)_2$	SO_3H
863	Cl	F	$B(OH)_2$	PO_3H_2
864	Cl	F	$B(OH)_2$	CHO
865	Cl	F	$B(OH)_2$	COOH

866	Cl	F	$B(OH)_2$	CH_2OH
867	Cl	F	$B(OH)_2$	sugar
868	Cl	F	$B(OH)_2$	C-glycosyl compound
869	Cl	F	SH	OH
870	Cl	F	SH	D-glucitol
871	Cl	F	SH	SO_3H
872	Cl	F	SH	PO_3H_2
873	Cl	F	SH	CHO
874	Cl	F	SH	COOH
875	Cl	F	SH	CH_2OH
876	Cl	F	SH	sugar
877	Cl	F	SH	C-glycosyl compound
878	Cl	F	OCH_3	OH
879	Cl	F	OCH_3	D-glucitol
880	Cl	F	OCH_3	SO_3H
881	Cl	F	OCH_3	PO_3H_2
882	Cl	F	OCH_3	CHO
883	Cl	F	OCH_3	COOH
884	Cl	F	OCH_3	CH_2OH
885	Cl	F	OCH_3	sugar
886	Cl	F	OCH_3	C-glycosyl compound
887	Cl	Cl	H	OH
888	Cl	Cl	H	D-glucitol
889	Cl	Cl	H	SO_3H
890	Cl	Cl	H	PO_3H_2
891	Cl	Cl	H	CHO
892	Cl	Cl	H	COOH
893	Cl	Cl	H	CH_2OH
894	Cl	Cl	H	sugar
895	Cl	Cl	H	C-glycosyl compound
896	Cl	Cl	OH	CHO
897	Cl	Cl	OH	COOH
898	Cl	Cl	OH	CH_2OH
899	Cl	Cl	OH	sugar
900	Cl	Cl	OH	C-glycosyl compound
901	Cl	Cl	CH_3	OH
902	Cl	Cl	CH_3	D-glucitol
903	Cl	Cl	CH_3	SO_3H

904	Cl	Cl	CH_3	PO_3H_2
905	Cl	Cl	CH_3	CHO
906	Cl	Cl	CH_3	COOH
907	Cl	Cl	CH_3	CH_2OH
908	Cl	Cl	CH_3	sugar
909	Cl	Cl	CH_3	C-glycosyl compound
910	Cl	Cl	Cl	OH
911	Cl	Cl	Cl	D-glucitol
912	Cl	Cl	Cl	SO_3H
913	Cl	Cl	Cl	PO_3H_2
914	Cl	Cl	Cl	CHO
915	Cl	Cl	Cl	COOH
916	Cl	Cl	Cl	CH_2OH
917	Cl	Cl	Cl	sugar
918	Cl	Cl	Cl	C-glycosyl compound
919	Cl	Cl	$B(OH)_2$	OH
920	Cl	Cl	$B(OH)_2$	D-glucitol
921	Cl	Cl	$B(OH)_2$	SO_3H
922	Cl	Cl	$B(OH)_2$	PO_3H_2
923	Cl	Cl	$B(OH)_2$	CHO
924	Cl	Cl	$B(OH)_2$	COOH
925	Cl	Cl	$B(OH)_2$	CH_2OH
926	Cl	Cl	$B(OH)_2$	sugar
927	Cl	Cl	$B(OH)_2$	C-glycosyl compound
928	Cl	Cl	SH	OH
929	Cl	Cl	SH	D-glucitol
930	Cl	Cl	SH	SO_3H
931	Cl	Cl	SH	PO_3H_2
932	Cl	Cl	SH	CHO
933	Cl	Cl	SH	COOH
934	Cl	Cl	SH	CH_2OH
935	Cl	Cl	SH	sugar
936	Cl	Cl	SH	C-glycosyl compound
937	Cl	Cl	OCH_3	OH
938	Cl	Cl	OCH_3	D-glucitol
939	Cl	Cl	OCH_3	SO_3H
940	Cl	Cl	OCH_3	PO_3H_2

941	Cl	Cl	OCH_3	CHO
942	Cl	Cl	OCH_3	COOH
943	Cl	Cl	OCH_3	CH_2OH
944	Cl	Cl	OCH_3	sugar
945	Cl	Cl	OCH_3	C-glycosyl compound
946	Cl	CN	H	OH
947	Cl	CN	H	D-glucitol
948	Cl	CN	H	SO_3H
949	Cl	CN	H	PO_3H_2
950	Cl	CN	H	CHO
951	Cl	CN	H	COOH
952	Cl	CN	H	CH_2OH
953	Cl	CN	H	sugar
954	Cl	CN	H	C-glycosyl compound
955	Cl	CN	OH	OH
956	Cl	CN	OH	D-glucitol
957	Cl	CN	OH	SO_3H
958	Cl	CN	OH	PO_3H_2
959	Cl	CN	OH	CHO
960	Cl	CN	OH	COOH
961	Cl	CN	OH	CH_2OH
962	Cl	CN	OH	sugar
963	Cl	CN	OH	C-glycosyl compound
964	Cl	CN	CH_3	OH
965	Cl	CN	CH_3	D-glucitol
966	Cl	CN	CH_3	SO_3H
967	Cl	CN	CH_3	PO_3H_2
968	Cl	CN	CH_3	CHO
969	Cl	CN	CH_3	COOH
970	Cl	CN	CH_3	CH_2OH
971	Cl	CN	CH_3	sugar
972	Cl	CN	CH_3	C-glycosyl compound
973	Cl	CN	Cl	OH
974	Cl	CN	Cl	D-glucitol
975	Cl	CN	Cl	SO_3H
976	Cl	CN	Cl	PO_3H_2
977	Cl	CN	Cl	CHO
978	Cl	CN	Cl	COOH

979	Cl	CN	Cl	CH_2OH
980	Cl	CN	Cl	sugar
981	Cl	CN	Cl	C-glycosyl compound
982	Cl	CN	$B(OH)_2$	OH
983	Cl	CN	$B(OH)_2$	D-glucitol
984	Cl	CN	$B(OH)_2$	SO_3H
985	Cl	CN	$B(OH)_2$	PO_3H_2
986	Cl	CN	$B(OH)_2$	CHO
987	Cl	CN	$B(OH)_2$	COOH
988	Cl	CN	$B(OH)_2$	CH_2OH
989	Cl	CN	$B(OH)_2$	sugar
990	Cl	CN	$B(OH)_2$	C-glycosyl compound
991	Cl	CN	SH	OH
992	Cl	CN	SH	D-glucitol
993	Cl	CN	SH	SO_3H
994	Cl	CN	SH	PO_3H_2
995	Cl	CN	SH	CHO
996	Cl	CN	SH	COOH
997	Cl	CN	SH	CH_2OH
998	Cl	CN	SH	sugar
999	Cl	CN	SH	C-glycosyl compound
1000	Cl	CN	OCH_3	OH
1001	Cl	CN	OCH_3	D-glucitol
1002	Cl	CN	OCH_3	SO_3H
1003	Cl	CN	OCH_3	PO_3H_2
1004	Cl	CN	OCH_3	CHO
1005	Cl	CN	OCH_3	COOH
1006	Cl	CN	OCH_3	CH_2OH
1007	Cl	CN	OCH_3	sugar
1008	Cl	CN	OCH_3	C-glycosyl compound
1009	Cl	CH_3[a]	H	OH
1010	Cl	CH_3[a]	H	D-glucitol
1011	Cl	CH_3[a]	H	SO_3H
1012	Cl	CH_3[a]	H	PO_3H_2
1013	Cl	CH_3[a]	H	CHO
1014	Cl	CH_3[a]	H	COOH

1015	Cl	CH_3[a]	H	CH_2OH
1016	Cl	CH_3[a]	H	sugar
1017	Cl	CH_3[a]	H	C-glycosyl compound
1018	Cl	CH_3[a]	OH	OH
1019	Cl	CH_3[a]	OH	D-glucitol
1020	Cl	CH_3[a]	OH	SO_3H
1021	Cl	CH_3[a]	OH	PO_3H_2
1022	Cl	CH_3[a]	OH	CHO
1023	Cl	CH_3[a]	OH	COOH
1024	Cl	CH_3[a]	OH	CH_2OH
1025	Cl	CH_3[a]	OH	sugar
1026	Cl	CH_3[a]	OH	C-glycosyl compound
1027	Cl	CH_3[a]	CH_3	OH
1028	Cl	CH_3[a]	CH_3	D-glucitol
1029	Cl	CH_3[a]	CH_3	SO_3H
1030	Cl	CH_3[a]	CH_3	PO_3H_2
1031	Cl	CH_3[a]	CH_3	CHO
1032	Cl	CH_3[a]	CH_3	COOH
1033	Cl	CH_3[a]	CH_3	CH_2OH
1034	Cl	CH_3[a]	CH_3	sugar
1035	Cl	CH_3[a]	CH_3	C-glycosyl compound
1036	Cl	CH_3[a]	Cl	OH
1037	Cl	CH_3[a]	Cl	D-glucitol
1038	Cl	CH_3[a]	Cl	SO_3H
1039	Cl	CH_3[a]	Cl	PO_3H_2
1040	Cl	CH_3[a]	Cl	CHO
1041	Cl	CH_3[a]	Cl	COOH
1042	Cl	CH_3[a]	Cl	CH_2OH
1043	Cl	CH_3[a]	Cl	sugar
1044	Cl	CH_3[a]	Cl	C-glycosyl compound
1045	Cl	CH_3[a]	$B(OH)_2$	OH
1046	Cl	CH_3[a]	$B(OH)_2$	D-glucitol
1047	Cl	CH_3[a]	$B(OH)_2$	SO_3H

1048	Cl	CH_3[a]	$B(OH)_2$	PO_3H_2
1049	Cl	CH_3[a]	$B(OH)_2$	CHO
1050	Cl	CH_3[a]	$B(OH)_2$	COOH
1051	Cl	CH_3[a]	$B(OH)_2$	CH_2OH
1052	Cl	CH_3[a]	$B(OH)_2$	sugar
1053	Cl	CH_3[a]	$B(OH)_2$	C-glycosyl compound
1054	Cl	CH_3[a]	SH	OH
1055	Cl	CH_3[a]	SH	D-glucitol
1056	Cl	CH_3[a]	SH	SO_3H
1057	Cl	CH_3[a]	SH	PO_3H_2
1058	Cl	CH_3[a]	SH	CHO
1059	Cl	CH_3[a]	SH	COOH
1060	Cl	CH_3[a]	SH	CH_2OH
1061	Cl	CH_3[a]	SH	sugar
1062	Cl	CH_3[a]	SH	C-glycosyl compound
1063	Cl	CH_3[a]	OCH_3	OH
1064	Cl	CH_3[a]	OCH_3	D-glucitol
1065	Cl	CH_3[a]	OCH_3	SO_3H
1066	Cl	CH_3[a]	OCH_3	PO_3H_2
1067	Cl	CH_3[a]	OCH_3	CHO
1068	Cl	CH_3[a]	OCH_3	COOH
1069	Cl	CH_3[a]	OCH_3	CH_2OH
1070	Cl	CH_3[a]	OCH_3	sugar
1071	Cl	CH_3[a]	OCH_3	C-glycosyl compound
1072	Cl	OCH_3[b]	H	OH
1073	Cl	OCH_3[b]	H	D-glucitol
1074	Cl	OCH_3[b]	H	SO_3H
1075	Cl	OCH_3[b]	H	PO_3H_2
1076	Cl	OCH_3[b]	H	CHO
1077	Cl	OCH_3[b]	H	COOH
1078	Cl	OCH_3[b]	H	CH_2OH
1079	Cl	OCH_3[b]	H	sugar
1080	Cl	OCH_3[b]	H	C-glycosyl compound

1081	Cl	OCH_3[b]	OH	OH
1082	Cl	OCH_3[b]	OH	D-glucitol
1083	Cl	OCH_3[b]	OH	SO_3H
1084	Cl	OCH_3[b]	OH	PO_3H_2
1085	Cl	OCH_3[b]	OH	CHO
1086	Cl	OCH_3[b]	OH	COOH
1087	Cl	OCH_3[b]	OH	CH_2OH
1088	Cl	OCH_3[b]	OH	sugar
1089	Cl	OCH_3[b]	OH	C-glycosyl compound
1090	Cl	OCH_3[b]	CH_3	OH
1091	Cl	OCH_3[b]	CH_3	D-glucitol
1092	Cl	OCH_3[b]	CH_3	SO_3H
1093	Cl	OCH_3[b]	CH_3	PO_3H_2
1094	Cl	OCH_3[b]	CH_3	CHO
1095	Cl	OCH_3[b]	CH_3	COOH
1096	Cl	OCH_3[b]	CH_3	CH_2OH
1097	Cl	OCH_3[b]	CH_3	sugar
1098	Cl	OCH_3[b]	CH_3	C-glycosyl compound
1099	Cl	OCH_3[b]	Cl	OH
1100	Cl	OCH_3[b]	Cl	D-glucitol
1101	Cl	OCH_3[b]	Cl	SO_3H
1102	Cl	OCH_3[b]	Cl	PO_3H_2
1103	Cl	OCH_3[b]	Cl	CHO
1104	Cl	OCH_3[b]	Cl	COOH
1105	Cl	OCH_3[b]	Cl	CH_2OH
1106	Cl	OCH_3[b]	Cl	sugar
1107	Cl	OCH_3[b]	Cl	C-glycosyl compound
1108	Cl	OCH_3[b]	$B(OH)_2$	OH
1109	Cl	OCH_3[b]	$B(OH)_2$	D-glucitol
1110	Cl	OCH_3[b]	$B(OH)_2$	SO_3H
1111	Cl	OCH_3[b]	$B(OH)_2$	PO_3H_2
1112	Cl	OCH_3[b]	$B(OH)_2$	CHO
1113	Cl	OCH_3[b]	$B(OH)_2$	COOH

1114	Cl	OCH_3[b]	$B(OH)_2$	CH_2OH
1115	Cl	OCH_3[b]	$B(OH)_2$	sugar
1116	Cl	OCH_3[b]	$B(OH)_2$	C-glycosyl compound
1117	Cl	OCH_3[b]	SH	OH
1118	Cl	OCH_3[b]	SH	D-glucitol
1119	Cl	OCH_3[b]	SH	SO_3H
1120	Cl	OCH_3[b]	SH	PO_3H_2
1121	Cl	OCH_3[b]	SH	CHO
1122	Cl	OCH_3[b]	SH	COOH
1123	Cl	OCH_3[b]	SH	CH_2OH
1124	Cl	OCH_3[b]	SH	sugar
1125	Cl	OCH_3[b]	SH	C-glycosyl compound
1126	Cl	OCH_3[b]	OCH_3	OH
1127	Cl	OCH_3[b]	OCH_3	D-glucitol
1128	Cl	OCH_3[b]	OCH_3	SO_3H
1129	Cl	OCH_3[b]	OCH_3	PO_3H_2
1130	Cl	OCH_3[b]	OCH_3	CHO
1131	Cl	OCH_3[b]	OCH_3	COOH
1132	Cl	OCH_3[b]	OCH_3	CH_2OH
1133	Cl	OCH_3[b]	OCH_3	sugar
1134	Cl	OCH_3[b]	OCH_3	C-glycosyl compound
1135	CN	H	H	OH
1136	CN	H	H	D-glucitol
1137	CN	H	H	SO_3H
1138	CN	H	H	PO_3H_2
1139	CN	H	H	CHO
1140	CN	H	H	COOH
1141	CN	H	H	CH_2OH
1142	CN	H	H	sugar
1143	CN	H	H	C-glycosyl compound
1144	CN	H	OH	OH
1145	CN	H	OH	D-glucitol
1146	CN	H	OH	SO_3H
1147	CN	H	OH	PO_3H_2
1148	CN	H	OH	CHO

1149	CN	H	OH	COOH
1150	CN	H	OH	CH_2OH
1151	CN	H	OH	sugar
1152	CN	H	OH	C-glycosyl compound
1153	CN	H	CH_3	OH
1154	CN	H	CH_3	D-glucitol
1155	CN	H	CH_3	SO_3H
1156	CN	H	CH_3	PO_3H_2
1157	CN	H	CH_3	CHO
1158	CN	H	CH_3	COOH
1159	CN	H	CH_3	CH_2OH
1160	CN	H	CH_3	sugar
1161	CN	H	CH_3	C-glycosyl compound
1162	CN	H	Cl	OH
1163	CN	H	Cl	D-glucitol
1164	CN	H	Cl	SO_3H
1165	CN	H	Cl	PO_3H_2
1166	CN	H	Cl	CHO
1167	CN	H	Cl	COOH
1168	CN	H	Cl	CH_2OH
1169	CN	H	Cl	sugar
1170	CN	H	Cl	C-glycosyl compound
1171	CN	H	$B(OH)_2$	OH
1172	CN	H	$B(OH)_2$	D-glucitol
1173	CN	H	$B(OH)_2$	SO_3H
1174	CN	H	$B(OH)_2$	PO_3H_2
1175	CN	H	$B(OH)_2$	CHO
1176	CN	H	$B(OH)_2$	COOH
1177	CN	H	$B(OH)_2$	CH_2OH
1178	CN	H	$B(OH)_2$	sugar
1179	CN	H	$B(OH)_2$	C-glycosyl compound
1180	CN	H	SH	OH
1181	CN	H	SH	D-glucitol
1182	CN	H	SH	SO_3H
1183	CN	H	SH	PO_3H_2
1184	CN	H	SH	CHO
1185	CN	H	SH	COOH

1186	CN	H	SH	CH_2OH
1187	CN	H	SH	sugar
1188	CN	H	SH	C-glycosyl compound
1189	CN	H	OCH_3	OH
1190	CN	H	OCH_3	D-glucitol
1191	CN	H	OCH_3	SO_3H
1192	CN	H	OCH_3	PO_3H_2
1193	CN	H	OCH_3	CHO
1194	CN	H	OCH_3	COOH
1195	CN	H	OCH_3	CH_2OH
1196	CN	H	OCH_3	sugar
1197	CN	H	OCH_3	C-glycosyl compound
1198	CN	F	H	OH
1199	CN	F	H	D-glucitol
1200	CN	F	H	SO_3H
1201	CN	F	H	PO_3H_2
1202	CN	F	H	CHO
1203	CN	F	H	COOH
1204	CN	F	H	CH_2OH
1205	CN	F	H	sugar
1206	CN	F	H	C-glycosyl compound
1207	CN	F	OH	OH
1208	CN	F	OH	D-glucitol
1209	CN	F	OH	SO_3H
1210	CN	F	OH	PO_3H_2
1211	CN	F	OH	CHO
1212	CN	F	OH	COOH
1213	CN	F	OH	CH_2OH
1214	CN	F	OH	sugar
1215	CN	F	OH	C-glycosyl compound
1216	CN	F	CH_3	OH
1217	CN	F	CH_3	D-glucitol
1218	CN	F	CH_3	SO_3H
1219	CN	F	CH_3	PO_3H_2
1220	CN	F	CH_3	CHO
1221	CN	F	CH_3	COOH
1222	CN	F	CH_3	CH_2OH

1223	CN	F	CH_3	sugar
1224	CN	F	CH_3	C-glycosyl compound
1225	CN	F	Cl	OH
1226	CN	F	Cl	D-glucitol
1227	CN	F	Cl	SO_3H
1228	CN	F	Cl	PO_3H_2
1229	CN	F	Cl	CHO
1230	CN	F	Cl	COOH
1231	CN	F	Cl	CH_2OH
1232	CN	F	Cl	sugar
1233	CN	F	Cl	C-glycosyl compound
1234	CN	F	$B(OH)_2$	OH
1235	CN	F	$B(OH)_2$	D-glucitol
1236	CN	F	$B(OH)_2$	SO_3H
1237	CN	F	$B(OH)_2$	PO_3H_2
1238	CN	F	$B(OH)_2$	CHO
1239	CN	F	$B(OH)_2$	COOH
1240	CN	F	$B(OH)_2$	CH_2OH
1241	CN	F	$B(OH)_2$	sugar
1242	CN	F	$B(OH)_2$	C-glycosyl compound
1243	CN	F	SH	OH
1244	CN	F	SH	D-glucitol
1245	CN	F	SH	SO_3H
1246	CN	F	SH	PO_3H_2
1247	CN	F	SH	CHO
1248	CN	F	SH	COOH
1249	CN	F	SH	CH_2OH
1250	CN	F	SH	sugar
1251	CN	F	SH	C-glycosyl compound
1252	CN	F	OCH_3	OH
1253	CN	F	OCH_3	D-glucitol
1254	CN	F	OCH_3	SO_3H
1255	CN	F	OCH_3	PO_3H_2
1256	CN	F	OCH_3	CHO
1257	CN	F	OCH_3	COOH
1258	CN	F	OCH_3	CH_2OH
1259	CN	F	OCH_3	sugar

1260	CN	F	OCH_3	C-glycosyl compound
1261	CN	Cl	H	OH
1262	CN	Cl	H	D-glucitol
1263	CN	Cl	H	SO_3H
1264	CN	Cl	H	PO_3H_2
1265	CN	Cl	H	CHO
1266	CN	Cl	H	COOH
1267	CN	Cl	H	CH_2OH
1268	CN	Cl	H	sugar
1269	CN	Cl	H	C-glycosyl compound
1270	CN	Cl	OH	OH
1271	CN	Cl	OH	D-glucitol
1272	CN	Cl	OH	SO_3H
1273	CN	Cl	OH	PO_3H_2
1274	CN	Cl	OH	CHO
1275	CN	Cl	OH	COOH
1276	CN	Cl	OH	CH_2OH
1277	CN	Cl	OH	sugar
1278	CN	Cl	OH	C-glycosyl compound
1279	CN	Cl	CH_3	OH
1280	CN	Cl	CH_3	D-glucitol
1281	CN	Cl	CH_3	SO_3H
1282	CN	Cl	CH_3	PO_3H_2
1283	CN	Cl	CH_3	CHO
1284	CN	Cl	CH_3	COOH
1285	CN	Cl	CH_3	CH_2OH
1286	CN	Cl	CH_3	sugar
1287	CN	Cl	CH_3	C-glycosyl compound
1288	CN	Cl	Cl	OH
1289	CN	Cl	Cl	D-glucitol
1290	CN	Cl	Cl	SO_3H
1291	CN	Cl	Cl	PO_3H_2
1292	CN	Cl	Cl	CHO
1293	CN	Cl	Cl	COOH
1294	CN	Cl	Cl	CH_2OH
1295	CN	Cl	Cl	sugar
1296	CN	Cl	Cl	C-glycosyl compound
1297	CN	Cl	$B(OH)_2$	OH

1298	CN	Cl	$B(OH)_2$	D-glucitol
1299	CN	Cl	$B(OH)_2$	SO_3H
1300	CN	Cl	$B(OH)_2$	PO_3H_2
1301	CN	Cl	$B(OH)_2$	CHO
1302	CN	Cl	$B(OH)_2$	COOH
1303	CN	Cl	$B(OH)_2$	CH_2OH
1304	CN	Cl	$B(OH)_2$	sugar
1305	CN	Cl	$B(OH)_2$	C-glycosyl compound
1306	CN	Cl	SH	OH
1307	CN	Cl	SH	D-glucitol
1308	CN	Cl	SH	SO_3H
1309	CN	Cl	SH	PO_3H_2
1310	CN	Cl	SH	CHO
1311	CN	Cl	SH	COOH
1312	CN	Cl	SH	CH_2OH
1313	CN	Cl	SH	sugar
1314	CN	Cl	SH	C-glycosyl compound
1315	CN	Cl	OCH_3	OH
1316	CN	Cl	OCH_3	D-glucitol
1317	CN	Cl	OCH_3	SO_3H
1318	CN	Cl	OCH_3	PO_3H_2
1319	CN	Cl	OCH_3	CHO
1320	CN	Cl	OCH_3	COOH
1321	CN	Cl	OCH_3	CH_2OH
1322	CN	Cl	OCH_3	sugar
1323	CN	Cl	OCH_3	C-glycosyl compound
1324	CN	CN	H	OH
1325	CN	CN	H	D-glucitol
1326	CN	CN	H	SO_3H
1327	CN	CN	H	PO_3H_2
1328	CN	CN	H	CHO
1329	CN	CN	H	COOH
1330	CN	CN	H	CH_2OH
1331	CN	CN	H	sugar
1332	CN	CN	H	C-glycosyl compound
1333	CN	CN	OH	OH
1334	CN	CN	OH	D-glucitol

1335	CN	CN	OH	SO_3H
1336	CN	CN	OH	PO_3H_2
1337	CN	CN	OH	CHO
1338	CN	CN	OH	COOH
1339	CN	CN	OH	CH_2OH
1340	CN	CN	OH	sugar
1341	CN	CN	OH	C-glycosyl compound
1342	CN	CN	CH_3	OH
1343	CN	CN	CH_3	D-glucitol
1344	CN	CN	CH_3	SO_3H
1345	CN	CN	CH_3	PO_3H_2
1346	CN	CN	CH_3	CHO
1347	CN	CN	CH_3	COOH
1348	CN	CN	CH_3	CH_2OH
1349	CN	CN	CH_3	sugar
1350	CN	CN	CH_3	C-glycosyl compound
1351	CN	CN	Cl	OH
1352	CN	CN	Cl	D-glucitol
1353	CN	CN	Cl	SO_3H
1354	CN	CN	Cl	PO_3H_2
1355	CN	CN	Cl	CHO
1356	CN	CN	Cl	COOH
1357	CN	CN	Cl	CH_2OH
1358	CN	CN	Cl	sugar
1359	CN	CN	Cl	C-glycosyl compound
1360	CN	CN	$B(OH)_2$	OH
1361	CN	CN	$B(OH)_2$	D-glucitol
1362	CN	CN	$B(OH)_2$	SO_3H
1363	CN	CN	$B(OH)_2$	PO_3H_2
1364	CN	CN	$B(OH)_2$	CHO
1365	CN	CN	$B(OH)_2$	COOH
1366	CN	CN	$B(OH)_2$	CH_2OH
1367	CN	CN	$B(OH)_2$	sugar
1368	CN	CN	$B(OH)_2$	C-glycosyl compound
1369	CN	CN	SH	OH
1370	CN	CN	SH	D-glucitol
1371	CN	CN	SH	SO_3H

1372	CN	CN	SH	PO_3H_2
1373	CN	CN	SH	CHO
1374	CN	CN	SH	COOH
1375	CN	CN	SH	CH_2OH
1376	CN	CN	SH	sugar
1377	CN	CN	SH	C-glycosyl compound
1378	CN	CN	OCH_3	OH
1379	CN	CN	OCH_3	D-glucitol
1380	CN	CN	OCH_3	SO_3H
1381	CN	CN	OCH_3	PO_3H_2
1382	CN	CN	OCH_3	CHO
1383	CN	CN	OCH_3	COOH
1384	CN	CN	OCH_3	CH_2OH
1385	CN	CN	OCH_3	sugar
1386	CN	CN	OCH_3	C-glycosyl compound
1387	CN	CH_3[a]	H	OH
1388	CN	CH_3[a]	H	D-glucitol
1389	CN	CH_3[a]	H	SO_3H
1390	CN	CH_3[a]	H	PO_3H_2
1391	CN	CH_3[a]	H	CHO
1392	CN	CH_3[a]	H	COOH
1393	CN	CH_3[a]	H	CH_2OH
1394	CN	CH_3[a]	H	sugar
1395	CN	CH_3[a]	H	C-glycosyl compound
1396	CN	CH_3[a]	OH	OH
1397	CN	CH_3[a]	OH	D-glucitol
1398	CN	CH_3[a]	OH	SO_3H
1399	CN	CH_3[a]	OH	PO_3H_2
1400	CN	CH_3[a]	OH	CHO
1401	CN	CH_3[a]	OH	COOH
1402	CN	CH_3[a]	OH	CH_2OH
1403	CN	CH_3[a]	OH	sugar
1404	CN	CH_3[a]	OH	C-glycosyl compound
1405	CN	CH_3[a]	CH_3	OH

1406	CN	CH_3[a]	CH_3	D-glucitol
1407	CN	CH_3[a]	CH_3	SO_3H
1408	CN	CH_3[a]	CH_3	PO_3H_2
1409	CN	CH_3[a]	CH_3	CHO
1410	CN	CH_3[a]	CH_3	COOH
1411	CN	CH_3[a]	CH_3	CH_2OH
1412	CN	CH_3[a]	CH_3	sugar
1413	CN	CH_3[a]	CH_3	C-glycosyl compound
1414	CN	CH_3[a]	Cl	OH
1415	CN	CH_3[a]	Cl	D-glucitol
1416	CN	CH_3[a]	Cl	SO_3H
1417	CN	CH_3[a]	Cl	PO_3H_2
1418	CN	CH_3[a]	Cl	CHO
1419	CN	CH_3[a]	Cl	COOH
1420	CN	CH_3[a]	Cl	CH_2OH
1421	CN	CH_3[a]	Cl	sugar
1422	CN	CH_3[a]	Cl	C-glycosyl compound
1423	CN	CH_3[a]	$B(OH)_2$	OH
1424	CN	CH_3[a]	$B(OH)_2$	D-glucitol
1425	CN	CH_3[a]	$B(OH)_2$	SO_3H
1426	CN	CH_3[a]	$B(OH)_2$	PO_3H_2
1427	CN	CH_3[a]	$B(OH)_2$	CHO
1428	CN	CH_3[a]	$B(OH)_2$	COOH
1429	CN	CH_3[a]	$B(OH)_2$	CH_2OH
1430	CN	CH_3[a]	$B(OH)_2$	sugar
1431	CN	CH_3[a]	$B(OH)_2$	C-glycosyl compound
1432	CN	CH_3[a]	SH	OH
1433	CN	CH_3[a]	SH	D-glucitol
1434	CN	CH_3[a]	SH	SO_3H
1435	CN	CH_3[a]	SH	PO_3H_2
1436	CN	CH_3[a]	SH	CHO
1437	CN	CH_3[a]	SH	COOH
1438	CN	CH_3[a]	SH	CH_2OH

1439	CN	CH_3^a	SH	sugar
1440	CN	CH_3^a	SH	C-glycosyl compound
1441	CN	CH_3^a	OCH_3	OH
1442	CN	CH_3^a	OCH_3	D-glucitol
1443	CN	CH_3^a	OCH_3	SO_3H
1444	CN	CH_3^a	OCH_3	PO_3H_2
1445	CN	CH_3^a	OCH_3	CHO
1446	CN	CH_3^a	OCH_3	COOH
1447	CN	CH_3^a	OCH_3	CH_2OH
1448	CN	CH_3^a	OCH_3	sugar
1449	CN	CH_3^a	OCH_3	C-glycosyl compound
1450	CN	OCH_3^b	H	OH
1451	CN	OCH_3^b	H	D-glucitol
1452	CN	OCH_3^b	H	SO_3H
1453	CN	OCH_3^b	H	PO_3H_2
1454	CN	OCH_3^b	H	CHO
1455	CN	OCH_3^b	H	COOH
1456	CN	OCH_3^b	H	CH_2OH
1457	CN	OCH_3^b	H	sugar
1458	CN	OCH_3^b	H	C-glycosyl compound
1459	CN	OCH_3^b	OH	OH
1460	CN	OCH_3^b	OH	D-glucitol
1461	CN	OCH_3^b	OH	SO_3H
1462	CN	OCH_3^b	OH	PO_3H_2
1463	CN	OCH_3^b	OH	CHO
1464	CN	OCH_3^b	OH	COOH
1465	CN	OCH_3^b	OH	CH_2OH
1466	CN	OCH_3^b	OH	sugar
1467	CN	OCH_3^b	OH	C-glycosyl compound
1468	CN	OCH_3^b	CH_3	OH
1469	CN	OCH_3^b	CH_3	D-glucitol
1470	CN	OCH_3^b	CH_3	SO_3H
1471	CN	OCH_3^b	CH_3	PO_3H_2

1472	CN	OCH_3[b]	CH_3	CHO
1473	CN	OCH_3[b]	CH_3	COOH
1474	CN	OCH_3[b]	CH_3	CH_2OH
1475	CN	OCH_3[b]	CH_3	sugar
1476	CN	OCH_3[b]	CH_3	C-glycosyl compound
1477	CN	OCH_3[b]	Cl	OH
1478	CN	OCH_3[b]	Cl	D-glucitol
1479	CN	OCH_3[b]	Cl	SO_3H
1480	CN	OCH_3[b]	Cl	PO_3H_2
1481	CN	OCH_3[b]	Cl	CHO
1482	CN	OCH_3[b]	Cl	COOH
1483	CN	OCH_3[b]	Cl	CH_2OH
1484	CN	OCH_3[b]	Cl	sugar
1485	CN	OCH_3[b]	Cl	C-glycosyl compound
1486	CN	OCH_3[b]	$B(OH)_2$	OH
1487	CN	OCH_3[b]	$B(OH)_2$	D-glucitol
1488	CN	OCH_3[b]	$B(OH)_2$	SO_3H
1489	CN	OCH_3[b]	$B(OH)_2$	PO_3H_2
1490	CN	OCH_3[b]	$B(OH)_2$	CHO
1491	CN	OCH_3[b]	$B(OH)_2$	COOH
1492	CN	OCH_3[b]	$B(OH)_2$	CH_2OH
1493	CN	OCH_3[b]	$B(OH)_2$	sugar
1494	CN	OCH_3[b]	$B(OH)_2$	C-glycosyl compound
1495	CN	OCH_3[b]	SH	OH
1496	CN	OCH_3[b]	SH	D-glucitol
1497	CN	OCH_3[b]	SH	SO_3H
1498	CN	OCH_3[b]	SH	PO_3H_2
1499	CN	OCH_3[b]	SH	CHO
1500	CN	OCH_3[b]	SH	COOH
1501	CN	OCH_3[b]	SH	CH_2OH
1502	CN	OCH_3[b]	SH	sugar
1503	CN	OCH_3[b]	SH	C-glycosyl compound
1504	CN	OCH_3[b]	OCH_3	OH

1505	CN	OCH_3[b]	OCH_3	D-glucitol
1506	CN	OCH_3[b]	OCH_3	SO_3H
1507	CN	OCH_3[b]	OCH_3	PO_3H_2
1508	CN	OCH_3[b]	OCH_3	CHO
1509	CN	OCH_3[b]	OCH_3	COOH
1510	CN	OCH_3[b]	OCH_3	CH_2OH
1511	CN	OCH_3[b]	OCH_3	sugar
1512	CN	OCH_3[b]	OCH_3	C-glycosyl compound
1513	CH_3[a]	H	H	OH
1514	CH_3[a]	H	H	D-glucitol
1515	CH_3[a]	H	H	SO_3H
1516	CH_3[a]	H	H	PO_3H_2
1517	CH_3[a]	H	H	CHO
1518	CH_3[a]	H	H	COOH
1519	CH_3[a]	H	H	CH_2OH
1520	CH_3[a]	H	H	sugar
1521	CH_3[a]	H	H	C-glycosyl compound
1522	CH_3[a]	H	OH	OH
1523	CH_3[a]	H	OH	D-glucitol
1524	CH_3[a]	H	OH	SO_3H
1525	CH_3[a]	H	OH	PO_3H_2
1526	CH_3[a]	H	OH	CHO
1527	CH_3[a]	H	OH	COOH
1528	CH_3[a]	H	OH	CH_2OH
1529	CH_3[a]	H	OH	sugar
1530	CH_3[a]	H	OH	C-glycosyl compound
1531	CH_3[a]	H	CH_3	OH
1532	CH_3[a]	H	CH_3	D-glucitol
1533	CH_3[a]	H	CH_3	SO_3H
1534	CH_3[a]	H	CH_3	PO_3H_2
1535	CH_3[a]	H	CH_3	CHO
1536	CH_3[a]	H	CH_3	COOH
1537	CH_3[a]	H	CH_3	CH_2OH

1538	$CH_3{}^a$	H	CH_3	sugar
1539	$CH_3{}^a$	H	CH_3	C-glycosyl compound
1540	$CH_3{}^a$	H	Cl	OH
1541	$CH_3{}^a$	H	Cl	D-glucitol
1542	$CH_3{}^a$	H	Cl	SO_3H
1543	$CH_3{}^a$	H	Cl	PO_3H_2
1544	$CH_3{}^a$	H	Cl	CHO
1545	$CH_3{}^a$	H	Cl	COOH
1546	$CH_3{}^a$	H	Cl	CH_2OH
1547	$CH_3{}^a$	H	Cl	sugar
1548	$CH_3{}^a$	H	Cl	C-glycosyl compound
1549	$CH_3{}^a$	H	$B(OH)_2$	OH
1550	$CH_3{}^a$	H	$B(OH)_2$	D-glucitol
1551	$CH_3{}^a$	H	$B(OH)_2$	SO_3H
1552	$CH_3{}^a$	H	$B(OH)_2$	PO_3H_2
1553	$CH_3{}^a$	H	$B(OH)_2$	CHO
1554	$CH_3{}^a$	H	$B(OH)_2$	COOH
1555	$CH_3{}^a$	H	$B(OH)_2$	CH_2OH
1556	$CH_3{}^a$	H	$B(OH)_2$	sugar
1557	$CH_3{}^a$	H	$B(OH)_2$	C-glycosyl compound
1558	$CH_3{}^a$	H	SH	OH
1559	$CH_3{}^a$	H	SH	D-glucitol
1560	$CH_3{}^a$	H	SH	SO_3H
1561	$CH_3{}^a$	H	SH	PO_3H_2
1562	$CH_3{}^a$	H	SH	CHO
1563	$CH_3{}^a$	H	SH	COOH
1564	$CH_3{}^a$	H	SH	CH_2OH
1565	$CH_3{}^a$	H	SH	sugar
1566	$CH_3{}^a$	H	SH	C-glycosyl compound
1567	$CH_3{}^a$	H	OCH_3	OH
1568	$CH_3{}^a$	H	OCH_3	D-glucitol
1569	$CH_3{}^a$	H	OCH_3	SO_3H
1570	$CH_3{}^a$	H	OCH_3	PO_3H_2

1571	CH_3[a]	H	OCH_3	CHO
1572	CH_3[a]	H	OCH_3	COOH
1573	CH_3[a]	H	OCH_3	CH_2OH
1574	CH_3[a]	H	OCH_3	sugar
1575	CH_3[a]	H	OCH_3	C-glycosyl compound
1576	CH_3[a]	F	H	OH
1577	CH_3[a]	F	H	D-glucitol
1578	CH_3[a]	F	H	SO_3H
1579	CH_3[a]	F	H	PO_3H_2
1580	CH_3[a]	F	H	CHO
1581	CH_3[a]	F	H	COOH
1582	CH_3[a]	F	H	CH_2OH
1583	CH_3[a]	F	H	sugar
1584	CH_3[a]	F	H	C-glycosyl compound
1585	CH_3[a]	F	OH	OH
1586	CH_3[a]	F	OH	D-glucitol
1587	CH_3[a]	F	OH	SO_3H
1588	CH_3[a]	F	OH	PO_3H_2
1589	CH_3[a]	F	OH	CHO
1590	CH_3[a]	F	OH	COOH
1591	CH_3[a]	F	OH	CH_2OH
1592	CH_3[a]	F	OH	sugar
1593	CH_3[a]	F	OH	C-glycosyl compound
1594	CH_3[a]	F	CH_3	OH
1595	CH_3[a]	F	CH_3	D-glucitol
1596	CH_3[a]	F	CH_3	SO_3H
1597	CH_3[a]	F	CH_3	PO_3H_2
1598	CH_3[a]	F	CH_3	CHO
1599	CH_3[a]	F	CH_3	COOH
1600	CH_3[a]	F	CH_3	CH_2OH
1601	CH_3[a]	F	CH_3	sugar
1602	CH_3[a]	F	CH_3	C-glycosyl compound
1603	CH_3[a]	F	Cl	OH

1604	CH_3[a]	F	Cl	D-glucitol
1605	CH_3[a]	F	Cl	SO_3H
1606	CH_3[a]	F	Cl	PO_3H_2
1607	CH_3[a]	F	Cl	CHO
1608	CH_3[a]	F	Cl	COOH
1609	CH_3[a]	F	Cl	CH_2OH
1610	CH_3[a]	F	Cl	sugar
1611	CH_3[a]	F	Cl	C-glycosyl compound
1612	CH_3[a]	F	$B(OH)_2$	OH
1613	CH_3[a]	F	$B(OH)_2$	D-glucitol
1614	CH_3[a]	F	$B(OH)_2$	SO_3H
1615	CH_3[a]	F	$B(OH)_2$	PO_3H_2
1616	CH_3[a]	F	$B(OH)_2$	CHO
1617	CH_3[a]	F	$B(OH)_2$	COOH
1618	CH_3[a]	F	$B(OH)_2$	CH_2OH
1619	CH_3[a]	F	$B(OH)_2$	sugar
1620	CH_3[a]	F	$B(OH)_2$	C-glycosyl compound
1621	CH_3[a]	F	SH	OH
1622	CH_3[a]	F	SH	D-glucitol
1623	CH_3[a]	F	SH	SO_3H
1624	CH_3[a]	F	SH	PO_3H_2
1625	CH_3[a]	F	SH	CHO
1626	CH_3[a]	F	SH	COOH
1627	CH_3[a]	F	SH	CH_2OH
1628	CH_3[a]	F	SH	sugar
1629	CH_3[a]	F	SH	C-glycosyl compound
1630	CH_3[a]	F	OCH_3	OH
1631	CH_3[a]	F	OCH_3	D-glucitol
1632	CH_3[a]	F	OCH_3	SO_3H
1633	CH_3[a]	F	OCH_3	PO_3H_2
1634	CH_3[a]	F	OCH_3	CHO
1635	CH_3[a]	F	OCH_3	COOH
1636	CH_3[a]	F	OCH_3	CH_2OH

1637	CH_3[a]	F	OCH_3	sugar
1638	CH_3[a]	F	OCH_3	C-glycosyl compound
1639	CH_3[a]	Cl	H	OH
1640	CH_3[a]	Cl	H	D-glucitol
1641	CH_3[a]	Cl	H	SO_3H
1642	CH_3[a]	Cl	H	PO_3H_2
1643	CH_3[a]	Cl	H	CHO
1644	CH_3[a]	Cl	H	COOH
1645	CH_3[a]	Cl	H	CH_2OH
1646	CH_3[a]	Cl	H	sugar
1647	CH_3[a]	Cl	H	C-glycosyl compound
1648	CH_3[a]	Cl	OH	OH
1649	CH_3[a]	Cl	OH	D-glucitol
1650	CH_3[a]	Cl	OH	SO_3H
1651	CH_3[a]	Cl	OH	PO_3H_2
1652	CH_3[a]	Cl	OH	CHO
1653	CH_3[a]	Cl	OH	COOH
1654	CH_3[a]	Cl	OH	CH_2OH
1655	CH_3[a]	Cl	OH	sugar
1656	CH_3[a]	Cl	OH	C-glycosyl compound
1657	CH_3[a]	Cl	CH_3	OH
1658	CH_3[a]	Cl	CH_3	D-glucitol
1659	CH_3[a]	Cl	CH_3	SO_3H
1660	CH_3[a]	Cl	CH_3	PO_3H_2
1661	CH_3[a]	Cl	CH_3	CHO
1662	CH_3[a]	Cl	CH_3	COOH
1663	CH_3[a]	Cl	CH_3	CH_2OH
1664	CH_3[a]	Cl	CH_3	sugar
1665	CH_3[a]	Cl	CH_3	C-glycosyl compound
1666	CH_3[a]	Cl	Cl	OH
1667	CH_3[a]	Cl	Cl	D-glucitol
1668	CH_3[a]	Cl	Cl	SO_3H
1669	CH_3[a]	Cl	Cl	PO_3H_2

1670	CH_3[a]	Cl	Cl	CHO
1671	CH_3[a]	Cl	Cl	COOH
1672	CH_3[a]	Cl	Cl	CH_2OH
1673	CH_3[a]	Cl	Cl	sugar
1674	CH_3[a]	Cl	Cl	C-glycosyl compound
1675	CH_3[a]	Cl	$B(OH)_2$	OH
1676	CH_3[a]	Cl	$B(OH)_2$	D-glucitol
1677	CH_3[a]	Cl	$B(OH)_2$	SO_3H
1678	CH_3[a]	Cl	$B(OH)_2$	PO_3H_2
1679	CH_3[a]	Cl	$B(OH)_2$	CHO
1680	CH_3[a]	Cl	$B(OH)_2$	COOH
1681	CH_3[a]	Cl	$B(OH)_2$	CH_2OH
1682	CH_3[a]	Cl	$B(OH)_2$	sugar
1683	CH_3[a]	Cl	$B(OH)_2$	C-glycosyl compound
1684	CH_3[a]	Cl	SH	OH
1685	CH_3[a]	Cl	SH	D-glucitol
1686	CH_3[a]	Cl	SH	SO_3H
1687	CH_3[a]	Cl	SH	PO_3H_2
1688	CH_3[a]	Cl	SH	CHO
1689	CH_3[a]	Cl	SH	COOH
1690	CH_3[a]	Cl	SH	CH_2OH
1691	CH_3[a]	Cl	SH	sugar
1692	CH_3[a]	Cl	SH	C-glycosyl compound
1693	CH_3[a]	Cl	OCH_3	OH
1694	CH_3[a]	Cl	OCH_3	D-glucitol
1695	CH_3[a]	Cl	OCH_3	SO_3H
1696	CH_3[a]	Cl	OCH_3	PO_3H_2
1697	CH_3[a]	Cl	OCH_3	CHO
1698	CH_3[a]	Cl	OCH_3	COOH
1699	CH_3[a]	Cl	OCH_3	CH_2OH
1700	CH_3[a]	Cl	OCH_3	sugar
1701	CH_3[a]	Cl	OCH_3	C-glycosyl compound
1702	CH_3[a]	CN	H	OH

1703	CH_3[a]	CN	H	D-glucitol
1704	CH_3[a]	CN	H	SO_3H
1705	CH_3[a]	CN	H	PO_3H_2
1706	CH_3[a]	CN	H	CHO
1707	CH_3[a]	CN	H	COOH
1708	CH_3[a]	CN	H	CH_2OH
1709	CH_3[a]	CN	H	sugar
1710	CH_3[a]	CN	H	C-glycosyl compound
1711	CH_3[a]	CN	OH	OH
1712	CH_3[a]	CN	OH	D-glucitol
1713	CH_3[a]	CN	OH	SO_3H
1714	CH_3[a]	CN	OH	PO_3H_2
1715	CH_3[a]	CN	OH	CHO
1716	CH_3[a]	CN	OH	COOH
1717	CH_3[a]	CN	OH	CH_2OH
1718	CH_3[a]	CN	OH	sugar
1719	CH_3[a]	CN	OH	C-glycosyl compound
1720	CH_3[a]	CN	CH_3	OH
1721	CH_3[a]	CN	CH_3	D-glucitol
1722	CH_3[a]	CN	CH_3	SO_3H
1723	CH_3[a]	CN	CH_3	PO_3H_2
1724	CH_3[a]	CN	CH_3	CHO
1725	CH_3[a]	CN	CH_3	COOH
1726	CH_3[a]	CN	CH_3	CH_2OH
1727	CH_3[a]	CN	CH_3	sugar
1728	CH_3[a]	CN	CH_3	C-glycosyl compound
1729	CH_3[a]	CN	Cl	OH
1730	CH_3[a]	CN	Cl	D-glucitol
1731	CH_3[a]	CN	Cl	SO_3H
1732	CH_3[a]	CN	Cl	PO_3H_2
1733	CH_3[a]	CN	Cl	CHO
1734	CH_3[a]	CN	Cl	COOH
1735	CH_3[a]	CN	Cl	CH_2OH

1736	CH_3[a]	CN	Cl	sugar
1737	CH_3[a]	CN	Cl	C-glycosyl compound
1738	CH_3[a]	CN	$B(OH)_2$	OH
1739	CH_3[a]	CN	$B(OH)_2$	D-glucitol
1740	CH_3[a]	CN	$B(OH)_2$	SO_3H
1741	CH_3[a]	CN	$B(OH)_2$	PO_3H_2
1742	CH_3[a]	CN	$B(OH)_2$	CHO
1743	CH_3[a]	CN	$B(OH)_2$	COOH
1744	CH_3[a]	CN	$B(OH)_2$	CH_2OH
1745	CH_3[a]	CN	$B(OH)_2$	sugar
1746	CH_3[a]	CN	$B(OH)_2$	C-glycosyl compound
1747	CH_3[a]	CN	SH	OH
1748	CH_3[a]	CN	SH	D-glucitol
1749	CH_3[a]	CN	SH	SO_3H
1750	CH_3[a]	CN	SH	PO_3H_2
1751	CH_3[a]	CN	SH	CHO
1752	CH_3[a]	CN	SH	COOH
1753	CH_3[a]	CN	SH	CH_2OH
1754	CH_3[a]	CN	SH	sugar
1755	CH_3[a]	CN	SH	C-glycosyl compound
1756	CH_3[a]	CN	OCH_3	OH
1757	CH_3[a]	CN	OCH_3	D-glucitol
1758	CH_3[a]	CN	OCH_3	SO_3H
1759	CH_3[a]	CN	OCH_3	PO_3H_2
1760	CH_3[a]	CN	OCH_3	CHO
1761	CH_3[a]	CN	OCH_3	COOH
1762	CH_3[a]	CN	OCH_3	CH_2OH
1763	CH_3[a]	CN	OCH_3	sugar
1764	CH_3[a]	CN	OCH_3	C-glycosyl compound
1765	CH_3[a]	CH_3[a]	H	OH
1766	CH_3[a]	CH_3[a]	H	D-glucitol
1767	CH_3[a]	CH_3[a]	H	SO_3H
1768	CH_3[a]	CH_3[a]	H	PO_3H_2

1769	CH_3[a]	CH_3[a]	H	CHO
1770	CH_3[a]	CH_3[a]	H	COOH
1771	CH_3[a]	CH_3[a]	H	CH_2OH
1772	CH_3[a]	CH_3[a]	H	sugar
1773	CH_3[a]	CH_3[a]	H	C-glycosyl compound
1774	CH_3[a]	CH_3[a]	OH	OH
1775	CH_3[a]	CH_3[a]	OH	D-glucitol
1776	CH_3[a]	CH_3[a]	OH	SO_3H
1777	CH_3[a]	CH_3[a]	OH	PO_3H_2
1778	CH_3[a]	CH_3[a]	OH	CHO
1779	CH_3[a]	CH_3[a]	OH	COOH
1780	CH_3[a]	CH_3[a]	OH	CH_2OH
1781	CH_3[a]	CH_3[a]	OH	sugar
1782	CH_3[a]	CH_3[a]	OH	C-glycosyl compound
1783	CH_3[a]	CH_3[a]	CH_3	OH
1784	CH_3[a]	CH_3[a]	CH_3	D-glucitol
1785	CH_3[a]	CH_3[a]	CH_3	SO_3H
1786	CH_3[a]	CH_3[a]	CH_3	PO_3H_2
1787	CH_3[a]	CH_3[a]	CH_3	CHO
1788	CH_3[a]	CH_3[a]	CH_3	COOH
1789	CH_3[a]	CH_3[a]	CH_3	CH_2OH
1790	CH_3[a]	CH_3[a]	CH_3	sugar
1791	CH_3[a]	CH_3[a]	CH_3	C-glycosyl compound
1792	CH_3[a]	CH_3[a]	Cl	OH
1793	CH_3[a]	CH_3[a]	Cl	D-glucitol
1794	CH_3[a]	CH_3[a]	Cl	SO_3H
1795	CH_3[a]	CH_3[a]	Cl	PO_3H_2
1796	CH_3[a]	CH_3[a]	Cl	CHO
1797	CH_3[a]	CH_3[a]	Cl	COOH
1798	CH_3[a]	CH_3[a]	Cl	CH_2OH
1799	CH_3[a]	CH_3[a]	Cl	sugar
1800	CH_3[a]	CH_3[a]	Cl	C-glycosyl compound
1801	CH_3[a]	CH_3[a]	$B(OH)_2$	OH

1802	CH_3[a]	CH_3[a]	$B(OH)_2$	D-glucitol
1803	CH_3[a]	CH_3[a]	$B(OH)_2$	SO_3H
1804	CH_3[a]	CH_3[a]	$B(OH)_2$	PO_3H_2
1805	CH_3[a]	CH_3[a]	$B(OH)_2$	CHO
1806	CH_3[a]	CH_3[a]	$B(OH)_2$	COOH
1807	CH_3[a]	CH_3[a]	$B(OH)_2$	CH_2OH
1808	CH_3[a]	CH_3[a]	$B(OH)_2$	sugar
1809	CH_3[a]	CH_3[a]	$B(OH)_2$	C-glycosyl compound
1810	CH_3[a]	CH_3[a]	SH	OH
1811	CH_3[a]	CH_3[a]	SH	D-glucitol
1812	CH_3[a]	CH_3[a]	SH	SO_3H
1813	CH_3[a]	CH_3[a]	SH	PO_3H_2
1814	CH_3[a]	CH_3[a]	SH	CHO
1815	CH_3[a]	CH_3[a]	SH	COOH
1816	CH_3[a]	CH_3[a]	SH	CH_2OH
1817	CH_3[a]	CH_3[a]	SH	sugar
1818	CH_3[a]	CH_3[a]	SH	C-glycosyl compound
1819	CH_3[a]	CH_3[a]	OCH_3	OH
1820	CH_3[a]	CH_3[a]	OCH_3	D-glucitol
1821	CH_3[a]	CH_3[a]	OCH_3	SO_3H
1822	CH_3[a]	CH_3[a]	OCH_3	PO_3H_2
1823	CH_3[a]	CH_3[a]	OCH_3	CHO
1824	CH_3[a]	CH_3[a]	OCH_3	COOH
1825	CH_3[a]	CH_3[a]	OCH_3	CH_2OH
1826	CH_3[a]	CH_3[a]	OCH_3	sugar
1827	CH_3[a]	CH_3[a]	OCH_3	C-glycosyl compound
1828	CH_3[a]	OCH_3[b]	H	OH
1829	CH_3[a]	OCH_3[b]	H	D-glucitol
1830	CH_3[a]	OCH_3[b]	H	SO_3H
1831	CH_3[a]	OCH_3[b]	H	PO_3H_2
1832	CH_3[a]	OCH_3[b]	H	CHO
1833	CH_3[a]	OCH_3[b]	H	COOH
1834	CH_3[a]	OCH_3[b]	H	CH_2OH

1835	CH_3[a]	OCH_3[b]	H	sugar
1836	CH_3[a]	OCH_3[b]	H	C-glycosyl compound
1837	CH_3[a]	OCH_3[b]	OH	OH
1838	CH_3[a]	OCH_3[b]	OH	D-glucitol
1839	CH_3[a]	OCH_3[b]	OH	SO_3H
1840	CH_3[a]	OCH_3[b]	OH	PO_3H_2
1841	CH_3[a]	OCH_3[b]	OH	CHO
1842	CH_3[a]	OCH_3[b]	OH	COOH
1843	CH_3[a]	OCH_3[b]	OH	CH_2OH
1844	CH_3[a]	OCH_3[b]	OH	sugar
1845	CH_3[a]	OCH_3[b]	OH	C-glycosyl compound
1846	CH_3[a]	OCH_3[b]	CH_3	OH
1847	CH_3[a]	OCH_3[b]	CH_3	D-glucitol
1848	CH_3[a]	OCH_3[b]	CH_3	SO_3H
1849	CH_3[a]	OCH_3[b]	CH_3	PO_3H_2
1850	CH_3[a]	OCH_3[b]	CH_3	CHO
1851	CH_3[a]	OCH_3[b]	CH_3	COOH
1852	CH_3[a]	OCH_3[b]	CH_3	CH_2OH
1853	CH_3[a]	OCH_3[b]	CH_3	sugar
1854	CH_3[a]	OCH_3[b]	CH_3	C-glycosyl compound
1855	CH_3[a]	OCH_3[b]	Cl	OH
1856	CH_3[a]	OCH_3[b]	Cl	D-glucitol
1857	CH_3[a]	OCH_3[b]	Cl	SO_3H
1858	CH_3[a]	OCH_3[b]	Cl	PO_3H_2
1859	CH_3[a]	OCH_3[b]	Cl	CHO
1860	CH_3[a]	OCH_3[b]	Cl	COOH
1861	CH_3[a]	OCH_3[b]	Cl	CH_2OH
1862	CH_3[a]	OCH_3[b]	Cl	sugar
1863	CH_3[a]	OCH_3[b]	Cl	C-glycosyl compound
1864	CH_3[a]	OCH_3[b]	$B(OH)_2$	OH
1865	CH_3[a]	OCH_3[b]	$B(OH)_2$	D-glucitol
1866	CH_3[a]	OCH_3[b]	$B(OH)_2$	SO_3H
1867	CH_3[a]	OCH_3[b]	$B(OH)_2$	PO_3H_2

1868	CH_3[a]	OCH_3[b]	$B(OH)_2$	CHO
1869	CH_3[a]	OCH_3[b]	$B(OH)_2$	COOH
1870	CH_3[a]	OCH_3[b]	$B(OH)_2$	CH_2OH
1871	CH_3[a]	OCH_3[b]	$B(OH)_2$	sugar
1872	CH_3[a]	OCH_3[b]	$B(OH)_2$	C-glycosyl compound
1873	CH_3[a]	OCH_3[b]	SH	OH
1874	CH_3[a]	OCH_3[b]	SH	D-glucitol
1875	CH_3[a]	OCH_3[b]	SH	SO_3H
1876	CH_3[a]	OCH_3[b]	SH	PO_3H_2
1877	CH_3[a]	OCH_3[b]	SH	CHO
1878	CH_3[a]	OCH_3[b]	SH	COOH
1879	CH_3[a]	OCH_3[b]	SH	CH_2OH
1880	CH_3[a]	OCH_3[b]	SH	sugar
1881	CH_3[a]	OCH_3[b]	SH	C-glycosyl compound
1882	CH_3[a]	OCH_3[b]	OCH_3	OH
1883	CH_3[a]	OCH_3[b]	OCH_3	D-glucitol
1884	CH_3[a]	OCH_3[b]	OCH_3	SO_3H
1885	CH_3[a]	OCH_3[b]	OCH_3	PO_3H_2
1886	CH_3[a]	OCH_3[b]	OCH_3	CHO
1887	CH_3[a]	OCH_3[b]	OCH_3	COOH
1888	CH_3[a]	OCH_3[b]	OCH_3	CH_2OH
1889	CH_3[a]	OCH_3[b]	OCH_3	sugar
1890	CH_3[a]	OCH_3[b]	OCH_3	C-glycosyl compound
1891	OCH_3[b]	H	H	OH
1892	OCH_3[b]	H	H	D-glucitol
1893	OCH_3[b]	H	H	SO_3H
1894	OCH_3[b]	H	H	PO_3H_2
1895	OCH_3[b]	H	H	CHO
1896	OCH_3[b]	H	H	COOH
1897	OCH_3[b]	H	H	CH_2OH
1898	OCH_3[b]	H	H	sugar
1899	OCH_3[b]	H	H	C-glycosyl compound
1900	OCH_3[b]	H	OH	OH

1901	OCH_3[b]	H	OH	D-glucitol
1902	OCH_3[b]	H	OH	SO_3H
1903	OCH_3[b]	H	OH	PO_3H_2
1904	OCH_3[b]	H	OH	CHO
1905	OCH_3[b]	H	OH	COOH
1906	OCH_3[b]	H	OH	CH_2OH
1907	OCH_3[b]	H	OH	sugar
1908	OCH_3[b]	H	OH	C-glycosyl compound
1909	OCH_3[b]	H	CH_3	OH
1910	OCH_3[b]	H	CH_3	D-glucitol
1911	OCH_3[b]	H	CH_3	SO_3H
1912	OCH_3[b]	H	CH_3	PO_3H_2
1913	OCH_3[b]	H	CH_3	CHO
1914	OCH_3[b]	H	CH_3	COOH
1915	OCH_3[b]	H	CH_3	CH_2OH
1916	OCH_3[b]	H	CH_3	sugar
1917	OCH_3[b]	H	CH_3	C-glycosyl compound
1918	OCH_3[b]	H	Cl	OH
1919	OCH_3[b]	H	Cl	D-glucitol
1920	OCH_3[b]	H	Cl	SO_3H
1921	OCH_3[b]	H	Cl	PO_3H_2
1922	OCH_3[b]	H	Cl	CHO
1923	OCH_3[b]	H	Cl	COOH
1924	OCH_3[b]	H	Cl	CH_2OH
1925	OCH_3[b]	H	Cl	sugar
1926	OCH_3[b]	H	Cl	C-glycosyl compound
1927	OCH_3[b]	H	$B(OH)_2$	OH
1928	OCH_3[b]	H	$B(OH)_2$	D-glucitol
1929	OCH_3[b]	H	$B(OH)_2$	SO_3H
1930	OCH_3[b]	H	$B(OH)_2$	PO_3H_2
1931	OCH_3[b]	H	$B(OH)_2$	CHO
1932	OCH_3[b]	H	$B(OH)_2$	COOH
1933	OCH_3[b]	H	$B(OH)_2$	CH_2OH
1934	OCH_3[b]	H	$B(OH)_2$	sugar

1935	OCH_3[b]	H	$B(OH)_2$	C-glycosyl compound
1936	OCH_3[b]	H	SH	OH
1937	OCH_3[b]	H	SH	D-glucitol
1938	OCH_3[b]	H	SH	SO_3H
1939	OCH_3[b]	H	SH	PO_3H_2
1940	OCH_3[b]	H	SH	CHO
1941	OCH_3[b]	H	SH	COOH
1942	OCH_3[b]	H	SH	CH_2OH
1943	OCH_3[b]	H	SH	sugar
1944	OCH_3[b]	H	SH	C-glycosyl compound
1945	OCH_3[b]	H	OCH_3	OH
1946	OCH_3[b]	H	OCH_3	D-glucitol
1947	OCH_3[b]	H	OCH_3	SO_3H
1948	OCH_3[b]	H	OCH_3	PO_3H_2
1949	OCH_3[b]	H	OCH_3	CHO
1950	OCH_3[b]	H	OCH_3	COOH
1951	OCH_3[b]	H	OCH_3	CH_2OH
1952	OCH_3[b]	H	OCH_3	sugar
1953	OCH_3[b]	H	OCH_3	C-glycosyl compound
1954	OCH_3[b]	F	H	OH
1955	OCH_3[b]	F	H	D-glucitol
1956	OCH_3[b]	F	H	SO_3H
1957	OCH_3[b]	F	H	PO_3H_2
1958	OCH_3[b]	F	H	CHO
1959	OCH_3[b]	F	H	COOH
1960	OCH_3[b]	F	H	CH_2OH
1961	OCH_3[b]	F	H	sugar
1962	OCH_3[b]	F	H	C-glycosyl compound
1963	OCH_3[b]	F	OH	OH
1964	OCH_3[b]	F	OH	D-glucitol
1965	OCH_3[b]	F	OH	SO_3H
1966	OCH_3[b]	F	OH	PO_3H_2
1967	OCH_3[b]	F	OH	CHO
1968	OCH_3[b]	F	OH	COOH

1969	OCH_3[b]	F	OH	CH_2OH
1970	OCH_3[b]	F	OH	sugar
1971	OCH_3[b]	F	OH	C-glycosyl compound
1972	OCH_3[b]	F	CH_3	OH
1973	OCH_3[b]	F	CH_3	D-glucitol
1974	OCH_3[b]	F	CH_3	SO_3H
1975	OCH_3[b]	F	CH_3	PO_3H_2
1976	OCH_3[b]	F	CH_3	CHO
1977	OCH_3[b]	F	CH_3	COOH
1978	OCH_3[b]	F	CH_3	CH_2OH
1979	OCH_3[b]	F	CH_3	sugar
1980	OCH_3[b]	F	CH_3	C-glycosyl compound
1981	OCH_3[b]	F	Cl	OH
1982	OCH_3[b]	F	Cl	D-glucitol
1983	OCH_3[b]	F	Cl	SO_3H
1984	OCH_3[b]	F	Cl	PO_3H_2
1985	OCH_3[b]	F	Cl	CHO
1986	OCH_3[b]	F	Cl	COOH
1987	OCH_3[b]	F	Cl	CH_2OH
1988	OCH_3[b]	F	Cl	sugar
1989	OCH_3[b]	F	Cl	C-glycosyl compound
1990	OCH_3[b]	F	$B(OH)_2$	OH
1991	OCH_3[b]	F	$B(OH)_2$	D-glucitol
1992	OCH_3[b]	F	$B(OH)_2$	SO_3H
1993	OCH_3[b]	F	$B(OH)_2$	PO_3H_2
1994	OCH_3[b]	F	$B(OH)_2$	CHO
1995	OCH_3[b]	F	$B(OH)_2$	COOH
1996	OCH_3[b]	F	$B(OH)_2$	CH_2OH
1997	OCH_3[b]	F	$B(OH)_2$	sugar
1998	OCH_3[b]	F	$B(OH)_2$	C-glycosyl compound
1999	OCH_3[b]	F	SH	OH
2000	OCH_3[b]	F	SH	D-glucitol
2001	OCH_3[b]	F	SH	SO_3H
2002	OCH_3[b]	F	SH	PO_3H_2

2003	OCH_3[b]	F	SH	CHO
2004	OCH_3[b]	F	SH	COOH
2005	OCH_3[b]	F	SH	CH_2OH
2006	OCH_3[b]	F	SH	sugar
2007	OCH_3[b]	F	SH	C-glycosyl compound
2008	OCH_3[b]	F	OCH_3	OH
2009	OCH_3[b]	F	OCH_3	D-glucitol
2010	OCH_3[b]	F	OCH_3	SO_3H
2011	OCH_3[b]	F	OCH_3	PO_3H_2
2012	OCH_3[b]	F	OCH_3	CHO
2013	OCH_3[b]	F	OCH_3	COOH
2014	OCH_3[b]	F	OCH_3	CH_2OH
2015	OCH_3[b]	F	OCH_3	sugar
2016	OCH_3[b]	F	OCH_3	C-glycosyl compound
2017	OCH_3[b]	Cl	H	OH
2018	OCH_3[b]	Cl	H	D-glucitol
2019	OCH_3[b]	Cl	H	SO_3H
2020	OCH_3[b]	Cl	H	PO_3H_2
2021	OCH_3[b]	Cl	H	CHO
2022	OCH_3[b]	Cl	H	COOH
2023	OCH_3[b]	Cl	H	CH_2OH
2024	OCH_3[b]	Cl	H	sugar
2025	OCH_3[b]	Cl	H	C-glycosyl compound
2026	OCH_3[b]	Cl	OH	OH
2027	OCH_3[b]	Cl	OH	D-glucitol
2028	OCH_3[b]	Cl	OH	SO_3H
2029	OCH_3[b]	Cl	OH	PO_3H_2
2030	OCH_3[b]	Cl	OH	CHO
2031	OCH_3[b]	Cl	OH	COOH
2032	OCH_3[b]	Cl	OH	CH_2OH
2033	OCH_3[b]	Cl	OH	sugar
2034	OCH_3[b]	Cl	OH	C-glycosyl compound
2035	OCH_3[b]	Cl	CH_3	OH
2036	OCH_3[b]	Cl	CH_3	D-glucitol

2037	OCH_3[b]	Cl	CH_3	SO_3H
2038	OCH_3[b]	Cl	CH_3	PO_3H_2
2039	OCH_3[b]	Cl	CH_3	CHO
2040	OCH_3[b]	Cl	CH_3	COOH
2041	OCH_3[b]	Cl	CH_3	CH_2OH
2042	OCH_3[b]	Cl	CH_3	sugar
2043	OCH_3[b]	Cl	CH_3	C-glycosyl compound
2044	OCH_3[b]	Cl	Cl	OH
2045	OCH_3[b]	Cl	Cl	D-glucitol
2046	OCH_3[b]	Cl	Cl	SO_3H
2047	OCH_3[b]	Cl	Cl	PO_3H_2
2048	OCH_3[b]	Cl	Cl	CHO
2049	OCH_3[b]	Cl	Cl	COOH
2050	OCH_3[b]	Cl	Cl	CH_2OH
2051	OCH_3[b]	Cl	Cl	sugar
2052	OCH_3[b]	Cl	Cl	C-glycosyl compound
2053	OCH_3[b]	Cl	$B(OH)_2$	OH
2054	OCH_3[b]	Cl	$B(OH)_2$	D-glucitol
2055	OCH_3[b]	Cl	$B(OH)_2$	SO_3H
2056	OCH_3[b]	Cl	$B(OH)_2$	PO_3H_2
2057	OCH_3[b]	Cl	$B(OH)_2$	CHO
2058	OCH_3[b]	Cl	$B(OH)_2$	COOH
2059	OCH_3[b]	Cl	$B(OH)_2$	CH_2OH
2060	OCH_3[b]	Cl	$B(OH)_2$	sugar
2061	OCH_3[b]	Cl	$B(OH)_2$	C-glycosyl compound
2062	OCH_3[b]	Cl	SH	OH
2063	OCH_3[b]	Cl	SH	D-glucitol
2064	OCH_3[b]	Cl	SH	SO_3H
2065	OCH_3[b]	Cl	SH	PO_3H_2
2066	OCH_3[b]	Cl	SH	CHO
2067	OCH_3[b]	Cl	SH	COOH
2068	OCH_3[b]	Cl	SH	CH_2OH
2069	OCH_3[b]	Cl	SH	sugar
2070	OCH_3[b]	Cl	SH	C-glycosyl compound

2071	OCH_3[b]	Cl	OCH_3	OH
2072	OCH_3[b]	Cl	OCH_3	D-glucitol
2073	OCH_3[b]	Cl	OCH_3	SO_3H
2074	OCH_3[b]	Cl	OCH_3	PO_3H_2
2075	OCH_3[b]	Cl	OCH_3	CHO
2076	OCH_3[b]	Cl	OCH_3	COOH
2077	OCH_3[b]	Cl	OCH_3	CH_2OH
2078	OCH_3[b]	Cl	OCH_3	sugar
2079	OCH_3[b]	Cl	OCH_3	C-glycosyl compound
2080	OCH_3[b]	CN	H	OH
2081	OCH_3[b]	CN	H	D-glucitol
2082	OCH_3[b]	CN	H	SO_3H
2083	OCH_3[b]	CN	H	PO_3H_2
2084	OCH_3[b]	CN	H	CHO
2085	OCH_3[b]	CN	H	COOH
2086	OCH_3[b]	CN	H	CH_2OH
2087	OCH_3[b]	CN	H	sugar
2088	OCH_3[b]	CN	H	C-glycosyl compound
2089	OCH_3[b]	CN	OH	OH
2090	OCH_3[b]	CN	OH	D-glucitol
2091	OCH_3[b]	CN	OH	SO_3H
2092	OCH_3[b]	CN	OH	PO_3H_2
2093	OCH_3[b]	CN	OH	CHO
2094	OCH_3[b]	CN	OH	COOH
2095	OCH_3[b]	CN	OH	CH_2OH
2096	OCH_3[b]	CN	OH	sugar
2097	OCH_3[b]	CN	OH	C-glycosyl compound
2098	OCH_3[b]	CN	CH_3	OH
2099	OCH_3[b]	CN	CH_3	D-glucitol
2100	OCH_3[b]	CN	CH_3	SO_3H
2101	OCH_3[b]	CN	CH_3	PO_3H_2
2102	OCH_3[b]	CN	CH_3	CHO
2103	OCH_3[b]	CN	CH_3	COOH
2104	OCH_3[b]	CN	CH_3	CH_2OH

2105	OCH_3[b]	CN	CH_3	sugar
2106	OCH_3[b]	CN	CH_3	C-glycosyl compound
2107	OCH_3[b]	CN	Cl	OH
2108	OCH_3[b]	CN	Cl	D-glucitol
2109	OCH_3[b]	CN	Cl	SO_3H
2110	OCH_3[b]	CN	Cl	PO_3H_2
2111	OCH_3[b]	CN	Cl	CHO
2112	OCH_3[b]	CN	Cl	COOH
2113	OCH_3[b]	CN	Cl	CH_2OH
2114	OCH_3[b]	CN	Cl	sugar
2115	OCH_3[b]	CN	Cl	C-glycosyl compound
2116	OCH_3[b]	CN	$B(OH)_2$	OH
2117	OCH_3[b]	CN	$B(OH)_2$	D-glucitol
2118	OCH_3[b]	CN	$B(OH)_2$	SO_3H
2119	OCH_3[b]	CN	$B(OH)_2$	PO_3H_2
2120	OCH_3[b]	CN	$B(OH)_2$	CHO
2121	OCH_3[b]	CN	$B(OH)_2$	COOH
2122	OCH_3[b]	CN	$B(OH)_2$	CH_2OH
2123	OCH_3[b]	CN	$B(OH)_2$	sugar
2124	OCH_3[b]	CN	$B(OH)_2$	C-glycosyl compound
2125	OCH_3[b]	CN	SH	OH
2126	OCH_3[b]	CN	SH	D-glucitol
2127	OCH_3[b]	CN	SH	SO_3H
2128	OCH_3[b]	CN	SH	PO_3H_2
2129	OCH_3[b]	CN	SH	CHO
2130	OCH_3[b]	CN	SH	COOH
2131	OCH_3[b]	CN	SH	CH_2OH
2132	OCH_3[b]	CN	SH	sugar
2133	OCH_3[b]	CN	SH	C-glycosyl compound
2134	OCH_3[b]	CN	OCH_3	OH
2135	OCH_3[b]	CN	OCH_3	D-glucitol
2136	OCH_3[b]	CN	OCH_3	SO_3H
2137	OCH_3[b]	CN	OCH_3	PO_3H_2
2138	OCH_3[b]	CN	OCH_3	CHO

2139	OCH_3[b]	CN	OCH_3	COOH
2140	OCH_3[b]	CN	OCH_3	CH_2OH
2141	OCH_3[b]	CN	OCH_3	sugar
2142	OCH_3[b]	CN	OCH_3	C-glycosyl compound
2143	OCH_3[b]	CH_3[a]	H	OH
2144	OCH_3[b]	CH_3[a]	H	D-glucitol
2145	OCH_3[b]	CH_3[a]	H	SO_3H
2146	OCH_3[b]	CH_3[a]	H	PO_3H_2
2147	OCH_3[b]	CH_3[a]	H	CHO
2148	OCH_3[b]	CH_3[a]	H	COOH
2149	OCH_3[b]	CH_3[a]	H	CH_2OH
2150	OCH_3[b]	CH_3[a]	H	sugar
2151	OCH_3[b]	CH_3[a]	H	C-glycosyl compound
2152	OCH_3[b]	CH_3[a]	OH	OH
2153	OCH_3[b]	CH_3[a]	OH	D-glucitol
2154	OCH_3[b]	CH_3[a]	OH	SO_3H
2155	OCH_3[b]	CH_3[a]	OH	PO_3H_2
2156	OCH_3[b]	CH_3[a]	OH	CHO
2157	OCH_3[b]	CH_3[a]	OH	COOH
2158	OCH_3[b]	CH_3[a]	OH	CH_2OH
2159	OCH_3[b]	CH_3[a]	OH	sugar
2160	OCH_3[b]	CH_3[a]	OH	C-glycosyl compound
2161	OCH_3[b]	CH_3[a]	CH_3	OH
2162	OCH_3[b]	CH_3[a]	CH_3	D-glucitol
2163	OCH_3[b]	CH_3[a]	CH_3	SO_3H
2164	OCH_3[b]	CH_3[a]	CH_3	PO_3H_2
2165	OCH_3[b]	CH_3[a]	CH_3	CHO
2166	OCH_3[b]	CH_3[a]	CH_3	COOH
2167	OCH_3[b]	CH_3[a]	CH_3	CH_2OH
2168	OCH_3[b]	CH_3[a]	CH_3	sugar
2169	OCH_3[b]	CH_3[a]	CH_3	C-glycosyl compound
2170	OCH_3[b]	CH_3[a]	Cl	OH
2171	OCH_3[b]	CH_3[a]	Cl	D-glucitol

2172	OCH_3[b]	CH_3[a]	Cl	SO_3H
2173	OCH_3[b]	CH_3[a]	Cl	PO_3H_2
2174	OCH_3[b]	CH_3[a]	Cl	CHO
2175	OCH_3[b]	CH_3[a]	Cl	COOH
2176	OCH_3[b]	CH_3[a]	Cl	CH_2OH
2177	OCH_3[b]	CH_3[a]	Cl	sugar
2178	OCH_3[b]	CH_3[a]	Cl	C-glycosyl compound
2179	OCH_3[b]	CH_3[a]	$B(OH)_2$	OH
2180	OCH_3[b]	CH_3[a]	$B(OH)_2$	D-glucitol
2181	OCH_3[b]	CH_3[a]	$B(OH)_2$	SO_3H
2182	OCH_3[b]	CH_3[a]	$B(OH)_2$	PO_3H_2
2183	OCH_3[b]	CH_3[a]	$B(OH)_2$	CHO
2184	OCH_3[b]	CH_3[a]	$B(OH)_2$	COOH
2185	OCH_3[b]	CH_3[a]	$B(OH)_2$	CH_2OH
2186	OCH_3[b]	CH_3[a]	$B(OH)_2$	sugar
2187	OCH_3[b]	CH_3[a]	$B(OH)_2$	C-glycosyl compound
2188	OCH_3[b]	CH_3[a]	SH	OH
2189	OCH_3[b]	CH_3[a]	SH	D-glucitol
2190	OCH_3[b]	CH_3[a]	SH	SO_3H
2191	OCH_3[b]	CH_3[a]	SH	PO_3H_2
2192	OCH_3[b]	CH_3[a]	SH	CHO
2193	OCH_3[b]	CH_3[a]	SH	COOH
2194	OCH_3[b]	CH_3[a]	SH	CH_2OH
2195	OCH_3[b]	CH_3[a]	SH	sugar
2196	OCH_3[b]	CH_3[a]	SH	C-glycosyl compound
2197	OCH_3[b]	CH_3[a]	OCH_3	OH
2198	OCH_3[b]	CH_3[a]	OCH_3	D-glucitol
2199	OCH_3[b]	CH_3[a]	OCH_3	SO_3H
2200	OCH_3[b]	CH_3[a]	OCH_3	PO_3H_2
2201	OCH_3[b]	CH_3[a]	OCH_3	CHO
2202	OCH_3[b]	CH_3[a]	OCH_3	COOH
2203	OCH_3[b]	CH_3[a]	OCH_3	CH_2OH
2204	OCH_3[b]	CH_3[a]	OCH_3	sugar

2205	OCH_3[b]	CH_3[a]	OCH_3	C-glycosyl compound
2206	OCH_3[b]	OCH_3[b]	H	OH
2207	OCH_3[b]	OCH_3[b]	H	D-glucitol
2208	OCH_3[b]	OCH_3[b]	H	SO_3H
2209	OCH_3[b]	OCH_3[b]	H	PO_3H_2
2210	OCH_3[b]	OCH_3[b]	H	CHO
2211	OCH_3[b]	OCH_3[b]	H	COOH
2212	OCH_3[b]	OCH_3[b]	H	CH_2OH
2213	OCH_3[b]	OCH_3[b]	H	sugar
2214	OCH_3[b]	OCH_3[b]	H	C-glycosyl compound
2215	OCH_3[b]	OCH_3[b]	OH	OH
2216	OCH_3[b]	OCH_3[b]	OH	D-glucitol
2217	OCH_3[b]	OCH_3[b]	OH	SO_3H
2218	OCH_3[b]	OCH_3[b]	OH	PO_3H_2
2219	OCH_3[b]	OCH_3[b]	OH	CHO
2220	OCH_3[b]	OCH_3[b]	OH	COOH
2221	OCH_3[b]	OCH_3[b]	OH	CH_2OH
2222	OCH_3[b]	OCH_3[b]	OH	sugar
2223	OCH_3[b]	OCH_3[b]	OH	C-glycosyl compound
2224	OCH_3[b]	OCH_3[b]	CH_3	OH
2225	OCH_3[b]	OCH_3[b]	CH_3	D-glucitol
2226	OCH_3[b]	OCH_3[b]	CH_3	SO_3H
2227	OCH_3[b]	OCH_3[b]	CH_3	PO_3H_2
2228	OCH_3[b]	OCH_3[b]	CH_3	CHO
2229	OCH_3[b]	OCH_3[b]	CH_3	COOH
2230	OCH_3[b]	OCH_3[b]	CH_3	CH_2OH
2231	OCH_3[b]	OCH_3[b]	CH_3	sugar
2232	OCH_3[b]	OCH_3[b]	CH_3	C-glycosyl compound
2233	OCH_3[b]	OCH_3[b]	Cl	OH
2234	OCH_3[b]	OCH_3[b]	Cl	D-glucitol
2235	OCH_3[b]	OCH_3[b]	Cl	SO_3H
2236	OCH_3[b]	OCH_3[b]	Cl	PO_3H_2
2237	OCH_3[b]	OCH_3[b]	Cl	CHO
2238	OCH_3[b]	OCH_3[b]	Cl	COOH

2239	OCH_3[b]	OCH_3[b]	Cl	CH_2OH
2240	OCH_3[b]	OCH_3[b]	Cl	sugar
2241	OCH_3[b]	OCH_3[b]	Cl	C-glycosyl compound
2242	OCH_3[b]	OCH_3[b]	$B(OH)_2$	OH
2243	OCH_3[b]	OCH_3[b]	$B(OH)_2$	D-glucitol
2244	OCH_3[b]	OCH_3[b]	$B(OH)_2$	SO_3H
2245	OCH_3[b]	OCH_3[b]	$B(OH)_2$	PO_3H_2
2246	OCH_3[b]	OCH_3[b]	$B(OH)_2$	CHO
2247	OCH_3[b]	OCH_3[b]	$B(OH)_2$	COOH
2248	OCH_3[b]	OCH_3[b]	$B(OH)_2$	CH_2OH
2249	OCH_3[b]	OCH_3[b]	$B(OH)_2$	sugar
2250	OCH_3[b]	OCH_3[b]	$B(OH)_2$	C-glycosyl compound
2251	OCH_3[b]	OCH_3[b]	SH	OH
2252	OCH_3[b]	OCH_3[b]	SH	D-glucitol
2253	OCH_3[b]	OCH_3[b]	SH	SO_3H
2254	OCH_3[b]	OCH_3[b]	SH	PO_3H_2
2255	OCH_3[b]	OCH_3[b]	SH	CHO
2256	OCH_3[b]	OCH_3[b]	SH	COOH
2257	OCH_3[b]	OCH_3[b]	SH	CH_2OH
2258	OCH_3[b]	OCH_3[b]	SH	sugar
2259	OCH_3[b]	OCH_3[b]	SH	C-glycosyl compound
2260	OCH_3[b]	OCH_3[b]	OCH_3	OH
2261	OCH_3[b]	OCH_3[b]	OCH_3	D-glucitol
2262	OCH_3[b]	OCH_3[b]	OCH_3	SO_3H
2263	OCH_3[b]	OCH_3[b]	OCH_3	PO_3H_2
2264	OCH_3[b]	OCH_3[b]	OCH_3	CHO
2265	OCH_3[b]	OCH_3[b]	OCH_3	COOH
2266	OCH_3[b]	OCH_3[b]	OCH_3	CH_2OH
2267	OCH_3[b]	OCH_3[b]	OCH_3	sugar
2268	OCH_3[b]	OCH_3[b]	OCH_3	C-glycosyl compound
2269	H	H	F	OH
2270	H	H	F	D-glucitol
2271	H	H	F	SO_3H
2272	H	H	F	PO_3H_2

2273	H	H	F	CHO
2274	H	H	F	COOH
2275	H	H	F	CH_2OH
2276	H	H	F	sugar
2277	H	H	F	C-glycosyl compound
2278	H	F	F	OH
2279	H	F	F	D-glucitol
2280	H	F	F	SO_3H
2281	H	F	F	PO_3H_2
2282	H	F	F	CHO
2283	H	F	F	COOH
2284	H	F	F	CH_2OH
2285	H	F	F	sugar
2286	H	F	F	C-glycosyl compound
2287	H	Cl	F	OH
2288	H	Cl	F	D-glucitol
2289	H	Cl	F	SO_3H
2290	H	Cl	F	PO_3H_2
2291	H	Cl	F	CHO
2292	H	Cl	F	COOH
2293	H	Cl	F	CH_2OH
2294	H	Cl	F	sugar
2295	H	Cl	F	C-glycosyl compound
2296	H	CN	F	OH
2297	H	CN	F	D-glucitol
2298	H	CN	F	SO_3H
2299	H	CN	F	PO_3H_2
2300	H	CN	F	CHO
2301	H	CN	F	COOH
2302	H	CN	F	CH_2OH
2303	H	CN	F	sugar
2304	H	CN	F	C-glycosyl compound
2305	H	CH_3[a]	F	OH
2306	H	CH_3[a]	F	D-glucitol
2307	H	CH_3[a]	F	SO_3H
2308	H	CH_3[a]	F	PO_3H_2
2309	H	CH_3[a]	F	CHO
2310	H	CH_3[a]	F	COOH

2311	H	CH_3[a]	F	CH_2OH
2312	H	CH_3[a]	F	sugar
2313	H	CH_3[a]	F	C-glycosyl compound
2314	H	OCH_3[b]	F	OH
2315	H	OCH_3[b]	F	D-glucitol
2316	H	OCH_3[b]	F	SO_3H
2317	H	OCH_3[b]	F	PO_3H_2
2318	H	OCH_3[b]	F	CHO
2319	H	OCH_3[b]	F	COOH
2320	H	OCH_3[b]	F	CH_2OH
2321	H	OCH_3[b]	F	sugar
2322	H	OCH_3[b]	F	C-glycosyl compound
2323	F	H	F	OH
2324	F	H	F	D-glucitol
2325	F	H	F	SO_3H
2326	F	H	F	PO_3H_2
2327	F	H	F	CHO
2328	F	H	F	COOH
2329	F	H	F	CH_2OH
2330	F	H	F	sugar
2331	F	H	F	C-glycosyl compound
2332	F	F	F	OH
2333	F	F	F	D-glucitol
2334	F	F	F	SO_3H
2335	F	F	F	PO_3H_2
2336	F	F	F	CHO
2337	F	F	F	COOH
2338	F	F	F	CH_2OH
2339	F	F	F	sugar
2340	F	F	F	C-glycosyl compound
2341	F	Cl	F	OH
2342	F	Cl	F	D-glucitol
2343	F	Cl	F	SO_3H
2344	F	Cl	F	PO_3H_2
2345	F	Cl	F	CHO
2346	F	Cl	F	COOH
2347	F	Cl	F	CH_2OH

2348	F	Cl	F	sugar
2349	F	Cl	F	C-glycosyl compound
2350	F	CN	F	OH
2351	F	CN	F	D-glucitol
2352	F	CN	F	SO_3H
2353	F	CN	F	PO_3H_2
2354	F	CN	F	CHO
2355	F	CN	F	COOH
2356	F	CN	F	CH_2OH
2357	F	CN	F	sugar
2358	F	CN	F	C-glycosyl compound
2359	F	CH_3[a]	F	OH
2360	F	CH_3[a]	F	D-glucitol
2361	F	CH_3[a]	F	SO_3H
2362	F	CH_3[a]	F	PO_3H_2
2363	F	CH_3[a]	F	CHO
2364	F	CH_3[a]	F	COOH
2365	F	CH_3[a]	F	CH_2OH
2366	F	CH_3[a]	F	sugar
2367	F	CH_3[a]	F	C-glycosyl compound
2368	F	OCH_3[b]	F	OH
2369	F	OCH_3[b]	F	D-glucitol
2370	F	OCH_3[b]	F	SO_3H
2371	F	OCH_3[b]	F	PO_3H_2
2372	F	OCH_3[b]	F	CHO
2373	F	OCH_3[b]	F	COOH
2374	F	OCH_3[b]	F	CH_2OH
2375	F	OCH_3[b]	F	sugar
2376	F	OCH_3[b]	F	C-glycosyl compound
2377	Cl	H	F	OH
2378	Cl	H	F	D-glucitol
2379	Cl	H	F	SO_3H
2380	Cl	H	F	PO_3H_2
2381	Cl	H	F	CHO
2382	Cl	H	F	COOH
2383	Cl	H	F	CH_2OH

2384	Cl	H	F	sugar
2385	Cl	H	F	C-glycosyl compound
2386	Cl	F	F	OH
2387	Cl	F	F	D-glucitol
2388	Cl	F	F	SO_3H
2389	Cl	F	F	PO_3H_2
2390	Cl	F	F	CHO
2391	Cl	F	F	COOH
2392	Cl	F	F	CH_2OH
2393	Cl	F	F	sugar
2394	Cl	F	F	C-glycosyl compound
2395	Cl	Cl	F	OH
2396	Cl	Cl	F	D-glucitol
2397	Cl	Cl	F	SO_3H
2398	Cl	Cl	F	PO_3H_2
2399	Cl	Cl	F	CHO
2400	Cl	Cl	F	COOH
2401	Cl	Cl	F	CH_2OH
2402	Cl	Cl	F	sugar
2403	Cl	Cl	F	C-glycosyl compound
2404	Cl	CN	F	OH
2405	Cl	CN	F	D-glucitol
2406	Cl	CN	F	SO_3H
2407	Cl	CN	F	PO_3H_2
2408	Cl	CN	F	CHO
2409	Cl	CN	F	COOH
2410	Cl	CN	F	CH_2OH
2411	Cl	CN	F	sugar
2412	Cl	CN	F	C-glycosyl compound
2413	Cl	CH_3[a]	F	OH
2414	Cl	CH_3[a]	F	D-glucitol
2415	Cl	CH_3[a]	F	SO_3H
2416	Cl	CH_3[a]	F	PO_3H_2
2417	Cl	CH_3[a]	F	CHO
2418	Cl	CH_3[a]	F	COOH
2419	Cl	CH_3[a]	F	CH_2OH
2420	Cl	CH_3[a]	F	sugar

2421	Cl	CH_3[a]	F	C-glycosyl compound
2422	Cl	OCH_3[b]	F	OH
2423	Cl	OCH_3[b]	F	D-glucitol
2424	Cl	OCH_3[b]	F	SO_3H
2425	Cl	OCH_3[b]	F	PO_3H_2
2426	Cl	OCH_3[b]	F	CHO
2427	Cl	OCH_3[b]	F	COOH
2428	Cl	OCH_3[b]	F	CH_2OH
2429	Cl	OCH_3[b]	F	sugar
2430	Cl	OCH_3[b]	F	C-glycosyl compound
2431	CN	H	F	OH
2432	CN	H	F	D-glucitol
2433	CN	H	F	SO_3H
2434	CN	H	F	PO_3H_2
2435	CN	H	F	CHO
2436	CN	H	F	COOH
2437	CN	H	F	CH_2OH
2438	CN	H	F	sugar
2439	CN	H	F	C-glycosyl compound
2440	CN	F	F	OH
2441	CN	F	F	D-glucitol
2442	CN	F	F	SO_3H
2443	CN	F	F	PO_3H_2
2444	CN	F	F	CHO
2445	CN	F	F	COOH
2446	CN	F	F	CH_2OH
2447	CN	F	F	sugar
2448	CN	F	F	C-glycosyl compound
2449	CN	Cl	F	OH
2450	CN	Cl	F	D-glucitol
2451	CN	Cl	F	SO_3H
2452	CN	Cl	F	PO_3H_2
2453	CN	Cl	F	CHO
2454	CN	Cl	F	COOH
2455	CN	Cl	F	CH_2OH
2456	CN	Cl	F	sugar
2457	CN	Cl	F	C-glycosyl compound
2458	CN	CN	F	OH

2459	CN	CN	F	D-glucitol
2460	CN	CN	F	SO_3H
2461	CN	CN	F	PO_3H_2
2462	CN	CN	F	CHO
2463	CN	CN	F	COOH
2464	CN	CN	F	CH_2OH
2465	CN	CN	F	sugar
2466	CN	CN	F	C-glycosyl compound
2467	CN	CH_3[a]	F	OH
2468	CN	CH_3[a]	F	D-glucitol
2469	CN	CH_3[a]	F	SO_3H
2470	CN	CH_3[a]	F	PO_3H_2
2471	CN	CH_3[a]	F	CHO
2472	CN	CH_3[a]	F	COOH
2473	CN	CH_3[a]	F	CH_2OH
2474	CN	CH_3[a]	F	sugar
2475	CN	CH_3[a]	F	C-glycosyl compound
2476	CN	OCH_3[b]	F	OH
2477	CN	OCH_3[b]	F	D-glucitol
2478	CN	OCH_3[b]	F	SO_3H
2479	CN	OCH_3[b]	F	PO_3H_2
2480	CN	OCH_3[b]	F	CHO
2481	CN	OCH_3[b]	F	COOH
2482	CN	OCH_3[b]	F	CH_2OH
2483	CN	OCH_3[b]	F	sugar
2484	CN	OCH_3[b]	F	C-glycosyl compound
2485	CH_3[a]	H	F	OH
2486	CH_3[a]	H	F	D-glucitol
2487	CH_3[a]	H	F	SO_3H
2488	CH_3[a]	H	F	PO_3H_2
2489	CH_3[a]	H	F	CHO
2490	CH_3[a]	H	F	COOH
2491	CH_3[a]	H	F	CH_2OH
2492	CH_3[a]	H	F	sugar

2493	CH_3[a]	H	F	C-glycosyl compound
2494	CH_3[a]	F	F	OH
2495	CH_3[a]	F	F	D-glucitol
2496	CH_3[a]	F	F	SO_3H
2497	CH_3[a]	F	F	PO_3H_2
2498	CH_3[a]	F	F	CHO
2499	CH_3[a]	F	F	COOH
2500	CH_3[a]	F	F	CH_2OH
2501	CH_3[a]	F	F	sugar
2502	CH_3[a]	F	F	C-glycosyl compound
2503	CH_3[a]	Cl	F	OH
2504	CH_3[a]	Cl	F	D-glucitol
2505	CH_3[a]	Cl	F	SO_3H
2506	CH_3[a]	Cl	F	PO_3H_2
2507	CH_3[a]	Cl	F	CHO
2508	CH_3[a]	Cl	F	COOH
2509	CH_3[a]	Cl	F	CH_2OH
2510	CH_3[a]	Cl	F	sugar
2511	CH_3[a]	Cl	F	C-glycosyl compound
2512	CH_3[a]	CN	F	OH
2513	CH_3[a]	CN	F	D-glucitol
2514	CH_3[a]	CN	F	SO_3H
2515	CH_3[a]	CN	F	PO_3H_2
2516	CH_3[a]	CN	F	CHO
2517	CH_3[a]	CN	F	COOH
2518	CH_3[a]	CN	F	CH_2OH
2519	CH_3[a]	CN	F	sugar
2520	CH_3[a]	CN	F	C-glycosyl compound
2521	CH_3[a]	CH_3[a]	F	OH
2522	CH_3[a]	CH_3[a]	F	D-glucitol
2523	CH_3[a]	CH_3[a]	F	SO_3H
2524	CH_3[a]	CH_3[a]	F	PO_3H_2
2525	CH_3[a]	CH_3[a]	F	CHO

2526	CH_3[a]	CH_3[a]	F	COOH
2527	CH_3[a]	CH_3[a]	F	CH_2OH
2528	CH_3[a]	CH_3[a]	F	sugar
2529	CH_3[a]	CH_3[a]	F	C-glycosyl compound
2530	CH_3[a]	OCH_3[b]	F	OH
2531	CH_3[a]	OCH_3[b]	F	D-glucitol
2532	CH_3[a]	OCH_3[b]	F	SO_3H
2533	CH_3[a]	OCH_3[b]	F	PO_3H_2
2534	CH_3[a]	OCH_3[b]	F	CHO
2535	CH_3[a]	OCH_3[b]	F	COOH
2536	CH_3[a]	OCH_3[b]	F	CH_2OH
2537	CH_3[a]	OCH_3[b]	F	sugar
2538	CH_3[a]	OCH_3[b]	F	C-glycosyl compound
2539	OCH_3[b]	H	F	OH
2540	OCH_3[b]	H	F	D-glucitol
2541	OCH_3[b]	H	F	SO_3H
2542	OCH_3[b]	H	F	PO_3H_2
2543	OCH_3[b]	H	F	CHO
2544	OCH_3[b]	H	F	COOH
2545	OCH_3[b]	H	F	CH_2OH
2546	OCH_3[b]	H	F	sugar
2547	OCH_3[b]	H	F	C-glycosyl compound
2548	OCH_3[b]	F	F	OH
2549	OCH_3[b]	F	F	D-glucitol
2550	OCH_3[b]	F	F	SO_3H
2551	OCH_3[b]	F	F	PO_3H_2
2552	OCH_3[b]	F	F	CHO
2553	OCH_3[b]	F	F	COOH
2554	OCH_3[b]	F	F	CH_2OH
2555	OCH_3[b]	F	F	sugar
2556	OCH_3[b]	F	F	C-glycosyl compound
2557	OCH_3[b]	Cl	F	OH
2558	OCH_3[b]	Cl	F	D-glucitol
2559	OCH_3[b]	Cl	F	SO_3H

2560	OCH_3[b]	Cl	F	PO_3H_2
2561	OCH_3[b]	Cl	F	CHO
2562	OCH_3[b]	Cl	F	COOH
2563	OCH_3[b]	Cl	F	CH_2OH
2564	OCH_3[b]	Cl	F	sugar
2565	OCH_3[b]	Cl	F	C-glycosyl compound
2566	OCH_3[b]	CN	F	OH
2567	OCH_3[b]	CN	F	D-glucitol
2568	OCH_3[b]	CN	F	SO_3H
2569	OCH_3[b]	CN	F	PO_3H_2
2570	OCH_3[b]	CN	F	CHO
2571	OCH_3[b]	CN	F	COOH
2572	OCH_3[b]	CN	F	CH_2OH
2573	OCH_3[b]	CN	F	sugar
2574	OCH_3[b]	CN	F	C-glycosyl compound
2575	OCH_3[b]	CH_3[a]	F	OH
2576	OCH_3[b]	CH_3[a]	F	D-glucitol
2577	OCH_3[b]	CH_3[a]	F	SO_3H
2578	OCH_3[b]	CH_3[a]	F	PO_3H_2
2579	OCH_3[b]	CH_3[a]	F	CHO
2580	OCH_3[b]	CH_3[a]	F	COOH
2581	OCH_3[b]	CH_3[a]	F	CH_2OH
2582	OCH_3[b]	CH_3[a]	F	sugar
2583	OCH_3[b]	CH_3[a]	F	C-glycosyl compound
2584	OCH_3[b]	OCH_3[b]	F	OH
2585	OCH_3[b]	OCH_3[b]	F	D-glucitol
2586	OCH_3[b]	OCH_3[b]	F	SO_3H
2587	OCH_3[b]	OCH_3[b]	F	PO_3H_2
2588	OCH_3[b]	OCH_3[b]	F	CHO
2589	OCH_3[b]	OCH_3[b]	F	COOH
2590	OCH_3[b]	OCH_3[b]	F	CH_2OH
2591	OCH_3[b]	OCH_3[b]	F	sugar
2592	OCH_3[b]	OCH_3[b]	F	C-glycosyl compound

[a] optionally substituted with one, two or three F

[b] optionally substituted with two or three F

Table 4

row number	R1	R2	R4	R5
1	ortho	ortho	3-	ortho
2	ortho	ortho	3-	meta
3	ortho	ortho	3-	para
4	ortho	ortho	2-	ortho
5	ortho	ortho	2-	meta
6	ortho	ortho	2-	para
7	ortho	meta	3-	ortho
8	ortho	meta	3-	meta
9	ortho	meta	3-	para
10	ortho	meta	2-	ortho
11	ortho	meta	2-	meta
12	ortho	meta	2-	para
13	ortho	para	3-	ortho
14	ortho	para	3-	meta
15	ortho	para	3-	para
16	ortho	para	2-	ortho
17	ortho	para	2-	meta
18	ortho	para	2-	para
19	meta	ortho	3-	ortho
20	meta	ortho	3-	meta
21	meta	ortho	3-	para
22	meta	ortho	2-	ortho
23	meta	ortho	2-	meta
24	meta	ortho	2-	para
25	meta	meta	3-	ortho
26	meta	meta	3-	meta

27	meta	meta	3-	para
28	meta	meta	2-	ortho
29	meta	meta	2-	meta
30	meta	meta	2-	para
31	meta	para	3-	ortho
32	meta	para	3-	meta
33	meta	para	3-	para
34	meta	para	2-	ortho
35	meta	para	2-	meta
36	meta	para	2-	para
37	para	ortho	3-	ortho
38	para	ortho	3-	meta
39	para	ortho	3-	para
40	para	ortho	2-	ortho
41	para	ortho	2-	meta
42	para	ortho	2-	para
43	para	meta	3-	ortho
44	para	meta	3-	meta
45	para	meta	3-	para
46	para	meta	2-	ortho
47	para	meta	2-	meta
48	para	meta	2-	para
49	para	para	3-	ortho
50	para	para	3-	meta
51	para	para	3-	para
52	para	para	2-	ortho
53	para	para	2-	meta
54	para	para	2-	para

[00445] Table 5 lists the compounds disclosed by substitution of Formula VIII wherein R^1 is H, R^2 is F, R^4 is OH and R^5 is OH (i.e. Table 3, row 1) according to the positions defined by all rows of Table 4.

1	(3R,4S)-4-(2',3-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
2	(3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
3	(3R,4S)-4-(3,4'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
4	(3R,4S)-4-(2,2'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
5	(3R,4S)-4-(2,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
6	(3R,4S)-4-(2,4'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
7	(3R,4S)-4-(2',3-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(3-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
8	(3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(3-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
9	(3R,4S)-4-(3,4'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(3-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
10	(3R,4S)-4-(2,2'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(3-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
11	(3R,4S)-4-(2,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(3-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
12	(3R,4S)-4-(2,4'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(3-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
13	(3R,4S)-4-(2',3-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
14	(3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one

15	(3R,4S)-4-(3,4'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
16	(3R,4S)-4-(2,2'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
17	(3R,4S)-4-(2,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
18	(3R,4S)-4-(2,4'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one

[00446] Table 6 lists the compounds disclosed by substitution of Formula VIII wherein R^1 is H, R^2 is F, R^4 is OH and R^5 is D-glucitol (i.e. Table 3, row 2) according to the positions defined by all rows of Table 4.

1	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-2-yl)-D-glucitol
2	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucitol
3	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol
4	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-2-yl)-D-glucitol
5	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-3-yl)-D-glucitol
6	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-4-yl)-D-glucitol
7	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(3-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-2-yl)-D-glucitol
8	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(3-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucitol
9	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(3-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol

10	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(3-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-2-yl)-D-glucitol
11	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(3-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-3-yl)-D-glucitol
12	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(3-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-4-yl)-D-glucitol
13	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-2-yl)-D-glucitol
14	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucitol
15	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol
16	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-2-yl)-D-glucitol
17	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-3-yl)-D-glucitol
18	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-4-yl)-D-glucitol

[00447] Table 7 lists the compounds disclosed by substitution of Formula VIII wherein R^1 is H, R^2 is F, R^4 is OH and R^5 is SO_3H (i.e. Table 3, row 3) according to the positions defined by all rows of Table 4.

1	4'-{(2S,3R)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-2-sulfonic acid
2	4'-{(2S,3R)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-sulfonic acid
3	4'-{(2S,3R)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-sulfonic acid
4	4'-{(2S,3R)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-2-sulfonic acid

5	4'-{(2S,3R)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-3-sulfonic acid
6	4'-{(2S,3R)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-4-sulfonic acid
7	4'-{(2S,3R)-3-[(3S)-3-(3-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-2-sulfonic acid
8	4'-{(2S,3R)-3-[(3S)-3-(3-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-sulfonic acid
9	4'-{(2S,3R)-3-[(3S)-3-(3-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-sulfonic acid
10	4'-{(2S,3R)-3-[(3S)-3-(3-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-2-sulfonic acid
11	4'-{(2S,3R)-3-[(3S)-3-(3-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-3-sulfonic acid
12	4'-{(2S,3R)-3-[(3S)-3-(3-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-4-sulfonic acid
13	4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-2-sulfonic acid
14	4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-sulfonic acid
15	4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-sulfonic acid
16	4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-2-sulfonic acid
17	4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-3-sulfonic acid
18	4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-4-sulfonic acid

[00448] Table 8 lists the compounds disclosed by substitution of Formula VIII wherein R^1 is H, R^2 is F, R^4 is OH and R^5 is PO_3H_2 (i.e. Table 3, row 4) according to the positions defined by all rows of Table 4.

1	(4'-{(2S,3R)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-2-yl)phosphonic acid
2	(4'-{(2S,3R)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)phosphonic acid
3	(4'-{(2S,3R)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid
4	(4'-{(2S,3R)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-2-yl)phosphonic acid
5	(4'-{(2S,3R)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-3-yl)phosphonic acid
6	(4'-{(2S,3R)-3-[(3S)-3-(2-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-4-yl)phosphonic acid
7	(4'-{(2S,3R)-3-[(3S)-3-(3-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-2-yl)phosphonic acid
8	(4'-{(2S,3R)-3-[(3S)-3-(3-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)phosphonic acid
9	(4'-{(2S,3R)-3-[(3S)-3-(3-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid
10	(4'-{(2S,3R)-3-[(3S)-3-(3-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-2-yl)phosphonic acid
11	(4'-{(2S,3R)-3-[(3S)-3-(3-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-3-yl)phosphonic acid
12	(4'-{(2S,3R)-3-[(3S)-3-(3-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-4-yl)phosphonic acid
13	(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-2-yl)phosphonic acid
14	(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)phosphonic acid

15	(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid
16	(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-2-yl)phosphonic acid
17	(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-3-yl)phosphonic acid
18	(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-4-yl)phosphonic acid

[00449] Table 9 lists the compounds disclosed by substitution of Formula VIII wherein R^1 is H, R^2 is H, R^4 is OH and R^5 is OH (i.e. Table 3, row 5) according to the positions defined by all rows of Table 4.

1	(3R,4S)-4-(2',3-dihydroxybiphenyl-4-yl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-1-phenylazetidin-2-one
2	(3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-1-phenylazetidin-2-one
3	(3R,4S)-4-(3,4'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-1-phenylazetidin-2-one
4	(3R,4S)-4-(2,2'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-1-phenylazetidin-2-one
5	(3R,4S)-4-(2,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-1-phenylazetidin-2-one
6	(3R,4S)-4-(2,4'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-1-phenylazetidin-2-one

[00450] Table 10 lists the compounds disclosed by substitution of Formula VIII wherein R^1 is H, R^2 is H, R^4 is OH and R^5 is D-glucitol (i.e. Table 3, row 6) according to the positions defined by all rows of Table 4.

1	(1S)-1,5-anhydro-1-(3'-hydroxy-4'-{(2S,3R)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-2-yl)-D-glucitol

2	(1S)-1,5-anhydro-1-(3'-hydroxy-4'-{(2S,3R)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)-D-glucitol
3	(1S)-1,5-anhydro-1-(3'-hydroxy-4'-{(2S,3R)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-4-yl)-D-glucitol
4	(1S)-1,5-anhydro-1-(2'-hydroxy-4'-{(2S,3R)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-2-yl)-D-glucitol
5	(1S)-1,5-anhydro-1-(2'-hydroxy-4'-{(2S,3R)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)-D-glucitol
6	(1S)-1,5-anhydro-1-(2'-hydroxy-4'-{(2S,3R)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-4-yl)-D-glucitol

[00451] Table 11 lists the compounds disclosed by substitution of Formula VIII wherein R^1 is H, R^2 is H, R^4 is OH and R^5 is SO_3H (i.e. Table 3, row 7) according to the positions defined by all rows of Table 4.

1	3'-hydroxy-4'-{(2S,3R)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-2-sulfonic acid
2	3'-hydroxy-4'-{(2S,3R)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-sulfonic acid
3	3'-hydroxy-4'-{(2S,3R)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-4-sulfonic acid
4	2'-hydroxy-4'-{(2S,3R)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-2-sulfonic acid
5	2'-hydroxy-4'-{(2S,3R)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-sulfonic acid
6	2'-hydroxy-4'-{(2S,3R)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-4-sulfonic acid

[00452] Table 12 lists the compounds disclosed by substitution of Formula VIII wherein R^1 is H, R^2 is H, R^4 is OH and R^5 is PO_3H_2 (i.e. Table 3, row 8) according to the positions defined by all rows of Table 4.

1	(3'-hydroxy-4'-{(2S,3R)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-2-yl)phosphonic acid
2	(3'-hydroxy-4'-{(2S,3R)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)phosphonic acid
3	(3'-hydroxy-4'-{(2S,3R)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-4-yl)phosphonic acid
4	(2'-hydroxy-4'-{(2S,3R)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-2-yl)phosphonic acid
5	(2'-hydroxy-4'-{(2S,3R)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)phosphonic acid
6	(2'-hydroxy-4'-{(2S,3R)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-4-yl)phosphonic acid

[00453] Table 13 lists the compounds disclosed by substitution of Formula VIII wherein R^1 is H, R^2 is Cl, R^4 is OH and R^5 is OH (i.e. Table 3, row 9) according to the positions defined by all rows of Table 4.

1	(3R,4S)-4-(2',3-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(2-chlorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
2	(3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(2-chlorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
3	(3R,4S)-4-(3,4'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(2-chlorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
4	(3R,4S)-4-(2,2'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(2-chlorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
5	(3R,4S)-4-(2,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(2-chlorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one

6	(3R,4S)-4-(2,4'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(2-chlorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
7	(3R,4S)-4-(2',3-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(3-chlorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
8	(3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(3-chlorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
9	(3R,4S)-4-(3,4'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(3-chlorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
10	(3R,4S)-4-(2,2'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(3-chlorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
11	(3R,4S)-4-(2,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(3-cjlorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
12	(3R,4S)-4-(2,4'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(3-chlorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
13	(3R,4S)-4-(2',3-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-chlorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
14	(3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-chlorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
15	(3R,4S)-4-(3,4'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-chlorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
16	(3R,4S)-4-(2,2'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-chlorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
17	(3R,4S)-4-(2,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-chlorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
18	(3R,4S)-4-(2,4'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4chlorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one

[00454] Table 14 lists the compounds disclosed by substitution of Formula VIII wherein R^1 is H, R^2 is Cl, R^4 is OH and R^5 is D-glucitol (i.e. Table 3, row 10) according to the positions defined by all rows of Table 4.

1	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(2-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-2-yl)-D-glucitol
2	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(2-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucitol
3	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(2-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol
4	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(2-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-2-yl)-D-glucitol
5	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(2-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-3-yl)-D-glucitol
6	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(2-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-4-yl)-D-glucitol
7	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(3-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-2-yl)-D-glucitol
8	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(3-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucitol
9	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(3-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol
10	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(3-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-2-yl)-D-glucitol
11	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(3-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-3-yl)-D-glucitol
12	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(3-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-4-yl)-D-glucitol
13	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-2-yl)-D-glucitol
14	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucitol
15	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol

16	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-2-yl)-D-glucitol
17	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-3-yl)-D-glucitol
18	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-4-yl)-D-glucitol

[00455] Table 15 lists the compounds disclosed by substitution of Formula VIII wherein R^1 is H, R^2 is Cl, R^4 is OH and R^5 is SO_3H (i.e. Table 3, row 11) according to the positions defined by all rows of Table 4.

1	4'-{(2S,3R)-3-[(3S)-3-(2-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-2-sulfonic acid
2	4'-{(2S,3R)-3-[(3S)-3-(2-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-sulfonic acid
3	4'-{(2S,3R)-3-[(3S)-3-(2-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-sulfonic acid
4	4'-{(2S,3R)-3-[(3S)-3-(2-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-2-sulfonic acid
5	4'-{(2S,3R)-3-[(3S)-3-(2-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-3-sulfonic acid
6	4'-{(2S,3R)-3-[(3S)-3-(2-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-4-sulfonic acid
7	4'-{(2S,3R)-3-[(3S)-3-(3-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-2-sulfonic acid
8	4'-{(2S,3R)-3-[(3S)-3-(3-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-sulfonic acid
9	4'-{(2S,3R)-3-[(3S)-3-(3-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-sulfonic acid
10	4'-{(2S,3R)-3-[(3S)-3-(3-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-2-sulfonic acid

11	4'-{(2S,3R)-3-[(3S)-3-(3-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-3-sulfonic acid
12	4'-{(2S,3R)-3-[(3S)-3-(3-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-4-sulfonic acid
13	4'-{(2S,3R)-3-[(3S)-3-(4-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-2-sulfonic acid
14	4'-{(2S,3R)-3-[(3S)-3-(4-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-sulfonic acid
15	4'-{(2S,3R)-3-[(3S)-3-(4-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-sulfonic acid
16	4'-{(2S,3R)-3-[(3S)-3-(4-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-2-sulfonic acid
17	4'-{(2S,3R)-3-[(3S)-3-(4-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-3-sulfonic acid
18	4'-{(2S,3R)-3-[(3S)-3-(4-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-4-sulfonic acid

[00456] Table 16 lists the compounds disclosed by substitution of Formula VIII wherein R^1 is H, R^2 is Cl, R^4 is OH and R^5 is PO_3H_2 (i.e. Table 3, row 12) according to the positions defined by all rows of Table 4.

1	(4'-{(2S,3R)-3-[(3S)-3-(2-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-2-yl)phosphonic acid
2	(4'-{(2S,3R)-3-[(3S)-3-(2-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)phosphonic acid
3	(4'-{(2S,3R)-3-[(3S)-3-(2-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid
4	(4'-{(2S,3R)-3-[(3S)-3-(2-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-2-yl)phosphonic acid
5	(4'-{(2S,3R)-3-[(3S)-3-(2-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-3-yl)phosphonic acid

6	(4'-{(2S,3R)-3-[(3S)-3-(2-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-4-yl)phosphonic acid
7	(4'-{(2S,3R)-3-[(3S)-3-(3-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-2-yl)phosphonic acid
8	(4'-{(2S,3R)-3-[(3S)-3-(3-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)phosphonic acid
9	(4'-{(2S,3R)-3-[(3S)-3-(3-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid
10	(4'-{(2S,3R)-3-[(3S)-3-(3-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-2-yl)phosphonic acid
11	(4'-{(2S,3R)-3-[(3S)-3-(3-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-3-yl)phosphonic acid
12	(4'-{(2S,3R)-3-[(3S)-3-(3-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-4-yl)phosphonic acid
13	(4'-{(2S,3R)-3-[(3S)-3-(4-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-2-yl)phosphonic acid
14	(4'-{(2S,3R)-3-[(3S)-3-(4-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)phosphonic acid
15	(4'-{(2S,3R)-3-[(3S)-3-(4-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid
16	(4'-{(2S,3R)-3-[(3S)-3-(4-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-2-yl)phosphonic acid
17	(4'-{(2S,3R)-3-[(3S)-3-(4-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-3-yl)phosphonic acid
18	(4'-{(2S,3R)-3-[(3S)-3-(4-chlorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-2'-hydroxybiphenyl-4-yl)phosphonic acid

[00457] Table 17 lists the compounds disclosed by substitution of Formula VIII wherein R^1 is F, R^2 is H, R^4 is OH and R^5 is OH (i.e. Table 3, row 13) according to the positions defined by all rows of Table 4.

1	(3R,4S)-4-(2',3-dihydroxybiphenyl-4-yl)-1-(2-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]azetidin-2-one
2	(3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-1-(2-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]azetidin-2-one
3	(3R,4S)-4-(3,4'-dihydroxybiphenyl-4-yl)-1-(2-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]azetidin-2-one
4	(3R,4S)-4-(2,2'-dihydroxybiphenyl-4-yl)-1-(2-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]azetidin-2-one
5	(3R,4S)-4-(2,3'-dihydroxybiphenyl-4-yl)-1-(2-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]azetidin-2-one
6	(3R,4S)-4-(2,4'-dihydroxybiphenyl-4-yl)-1-(2-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]azetidin-2-one
7	(3R,4S)-4-(2',3-dihydroxybiphenyl-4-yl)-1-(3-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]azetidin-2-one
8	(3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-1-(3-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]azetidin-2-one
9	(3R,4S)-4-(3,4'-dihydroxybiphenyl-4-yl)-1-(3-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]azetidin-2-one
10	(3R,4S)-4-(2,2'-dihydroxybiphenyl-4-yl)-1-(3-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]azetidin-2-one
11	(3R,4S)-4-(2,3'-dihydroxybiphenyl-4-yl)-1-(3-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]azetidin-2-one
12	(3R,4S)-4-(2,4'-dihydroxybiphenyl-4-yl)-1-(3-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]azetidin-2-one
13	(3R,4S)-4-(2',3-dihydroxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]azetidin-2-one
14	(3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]azetidin-2-one
15	(3R,4S)-4-(3,4'-dihydroxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]azetidin-2-one

16	(3R,4S)-4-(2,2'-dihydroxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]azetidin-2-one
17	(3R,4S)-4-(2,3'-dihydroxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]azetidin-2-one
18	(3R,4S)-4-(2,4'-dihydroxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]azetidin-2-one

[00458] Table 18 lists the compounds disclosed by substitution of Formula VIII wherein R^1 is F, R^2 is H, R^4 is OH and R^5 is D-glucitol (i.e. Table 3, row 14) according to the positions defined by all rows of Table 4.

1	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-1-(2-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-2-yl)-D-glucitol
2	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-1-(2-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucitol
3	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-1-(2-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol
4	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-1-(2-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-2-yl)-D-glucitol
5	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-1-(2-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-3-yl)-D-glucitol
6	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-1-(2-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-4-yl)-D-glucitol
7	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-1-(3-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-2-yl)-D-glucitol
8	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-1-(3-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucitol
9	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-1-(3-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol
10	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-1-(3-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-2-yl)-D-glucitol

11	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-1-(3-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-3-yl)-D-glucitol
12	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-1-(3-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-4-yl)-D-glucitol
13	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-2-yl)-D-glucitol
14	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucitol
15	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol
16	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-2-yl)-D-glucitol
17	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-3-yl)-D-glucitol
18	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-4-yl)-D-glucitol

[00459] Table 19 lists the compounds disclosed by substitution of Formula VIII wherein R^1 is F, R^2 is H, R^4 is OH and R^5 is SO_3H (i.e. Table 3, row 15) according to the positions defined by all rows of Table 4.

1	4'-{(2S,3R)-1-(2-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-2-sulfonic acid
2	4'-{(2S,3R)-1-(2-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-3-sulfonic acid
3	4'-{(2S,3R)-1-(2-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-4-sulfonic acid
4	4'-{(2S,3R)-1-(2-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-2-sulfonic acid
5	4'-{(2S,3R)-1-(2-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-3-sulfonic acid

6	4'-{(2S,3R)-1-(2-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-4-sulfonic acid
7	4'-{(2S,3R)-1-(3-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-2-sulfonic acid
8	4'-{(2S,3R)-1-(3-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-3-sulfonic acid
9	4'-{(2S,3R)-1-(3-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-4-sulfonic acid
10	4'-{(2S,3R)-1-(3-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-2-sulfonic acid
11	4'-{(2S,3R)-1-(3-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-3-sulfonic acid
12	4'-{(2S,3R)-1-(3-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-4-sulfonic acid
13	4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-2-sulfonic acid
14	4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-3-sulfonic acid
15	4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-4-sulfonic acid
16	4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-2-sulfonic acid
17	4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-3-sulfonic acid
18	4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-4-sulfonic acid

[00460] Table 20 lists the compounds disclosed by substitution of Formula VIII wherein R^1 is F, R^2 is H, R^4 is OH and R^5 is PO_3H_2 (i.e. Table 3, row 16) according to the positions defined by all rows of Table 4.

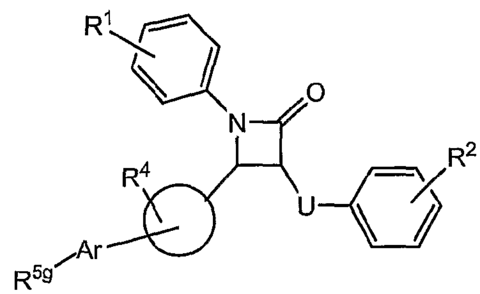
1	(4'-{(2S,3R)-1-(2-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-2-yl)phosphonic acid
2	(4'-{(2S,3R)-1-(2-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)phosphonic acid
3	(4'-{(2S,3R)-1-(2-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid
4	(4'-{(2S,3R)-1-(2-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-2-yl)phosphonic acid
5	(4'-{(2S,3R)-1-(2-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-3-yl)phosphonic acid
6	(4'-{(2S,3R)-1-(2-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-4-yl)phosphonic acid
7	(4'-{(2S,3R)-1-(3-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-2-yl)phosphonic acid
8	(4'-{(2S,3R)-1-(3-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)phosphonic acid
9	(4'-{(2S,3R)-1-(3-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid
10	(4'-{(2S,3R)-1-(3-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-2-yl)phosphonic acid
11	(4'-{(2S,3R)-1-(3-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-3-yl)phosphonic acid
12	(4'-{(2S,3R)-1-(3-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-4-yl)phosphonic acid
13	(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-2-yl)phosphonic acid

14	(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)phosphonic acid
15	(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid
16	(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-2-yl)phosphonic acid
17	(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-3-yl)phosphonic acid
18	(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-phenylpropyl]-4-oxoazetidin-2-yl}-2'-hydroxybiphenyl-4-yl)phosphonic acid

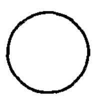
CLAIMS

We claim:

1. A compound of formula:



wherein

 represents an aryl or heteroaryl residue;

Ar represents an aryl residue;

R^1 represents one, two, three, four or five residues chosen independently from H, halogen, -OH, loweralkyl, OCF_2H, OCF_3, CF_2H, CH_2F, -O-loweralkyl, methylenedioxy, ethylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -SH, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, alkoxycarbonyl, carboxyalkyl, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy, $-PO_3H_2$, $-SO_3H$, $-B(OH)_2$, a sugar, a polyol, a glucuronide and a sugar carbamate;

R^2 represents one, two, three, four or five residues chosen independently from H, halogen, -OH, loweralkyl, OCF_2H, OCF_3, CF_2H, CH_2F, -O-loweralkyl, methylenedioxy, ethylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -SH, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, alkoxycarbonyl, carboxyalkyl, carboxamido, alkylsulfoxide, acylamino, amidino, $-PO_3H_2$, $-SO_3H$, $-B(OH)_2$, a sugar, a polyol, a glucuronide and a sugar carbamate;

R^4 represents one, two, three or four residues chosen independently from H, halogen, -OH, loweralkyl, -O-loweralkyl, hydroxyloweralkyl, -CN, CF_3, nitro, -SH, -S-

loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, alkoxycarbonyl, carboxyalkyl, carboxamido, alkylsulfoxide, acylamino, amidino, $-PO_3H_2$, $-SO_3H$, $-B(OH)_2$, a sugar, a polyol, a glucuronide and a sugar carbamate;

R^{5g} represents one, two, three, four or five residues on Ar chosen independently from halogen, -OH, loweralkyl, -O-loweralkyl, methylenedioxy, ethylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -SH, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, alkoxycarbonyl, carboxyalkyl, carboxamido, alkylsulfoxide, acylamino, amidino, $-PO_3H_2$, $-SO_3H$, $-B(OH)_2$, a sugar, a polyol, a glucuronide and a sugar carbamate;

U is $(C_2\text{-}C_6)$-alkylene in which one or more $-CH_2-$ may be replaced by a radical chosen from -S-, -S(O)-, $-SO_2-$, -O-, -C(=O)-, -CHOH-, -NH-, CHF, CF_2, -CH(O-loweralkyl)-, -CH(O-loweracyl)-, $-CH(OSO_3H)-$, $-CH(OPO_3H_2)-$, $-CH(OB(OH)_2)-$, or -NOH-;

with the provisos that

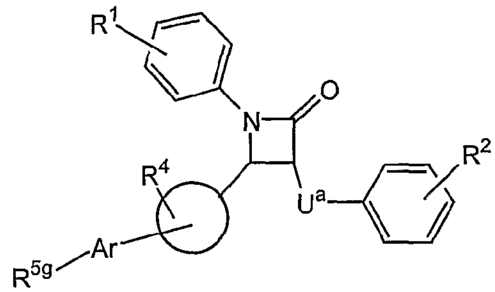
(1) R^{5g} cannot be -CN; 2,5-dimethoxy; 2,6-dimethoxy or halogen when neither R^4 nor R^{5g} is -OH, amino, loweralkyl, O-loweralkyl, alkoxycarbonyl, $-B(OH)_2$, $-PO_3H_2$ or $-SO_3H$ group;

(2) R^{5g} cannot be 2-hydroxy when  represents a 2,5-thienyl residue;

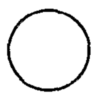
(3) adjacent $-CH_2-$ residues in U cannot be replaced by -S-, -S(O)-, $-SO_2-$ or -O- ; and

(4) -S-, -S(O)-, $-SO_2-$, -O- and -NH- residues in U cannot be separated only by a single carbon.

2. A compound of formula:



wherein

 represents an aryl or heteroaryl residue;

Ar represents an aryl residue;

R^1 represents one, two, three, four or five residues chosen independently from H, halogen, -OH, loweralkyl, OCF_2H, OCF_3, CF_2H, CH_2F, -O-loweralkyl, methylenedioxy, ethylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -SH, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, alkoxycarbonyl, carboxyalkyl, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy, $-PO_3H_2$, $-SO_3H$, $-B(OH)_2$, a sugar, a polyol, a glucuronide and a sugar carbamate;

R^2 represents one, two, three, four or five residues chosen independently from H, halogen, -OH, loweralkyl, OCF_2H, OCF_3, CF_2H, CH_2F, -O-loweralkyl, methylenedioxy, ethylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -SH, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, alkoxycarbonyl, carboxyalkyl, carboxamido, alkylsulfoxide, acylamino, amidino, $-PO_3H_2$, $-SO_3H$, $-B(OH)_2$, a sugar, a polyol, a glucuronide and a sugar carbamate;

R^4 represents one, two, three or four residues chosen independently from H, halogen, -OH, loweralkyl, -O-loweralkyl, hydroxyloweralkyl, -CN, CF_3, nitro, -SH, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, alkoxycarbonyl, carboxyalkyl, carboxamido, alkylsulfoxide, acylamino, amidino, $-PO_3H_2$, $-SO_3H$, -

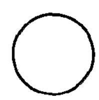
$B(OH)_2$, a sugar, a polyol, a glucuronide and a sugar carbamate;

R^{5g} represents from one to five residues on Ar chosen independently from halogen, -OH, loweralkyl, -O-loweralkyl, methylenedioxy, ethylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -SH, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, alkoxycarbonyl, carboxyalkyl, carboxamido, alkylsulfoxide, acylamino, amidino, $-PO_3H_2$, $-SO_3H$, $-B(OH)_2$, a sugar, a polyol, a glucuronide and a sugar carbamate;

U^a is (C_2-C_6)-alkylene in which one or more $-CH_2-$ may be replaced by a radical chosen from -S-, -S(O)-, $-SO_2-$, -O-, -C(=O)-, -CHOH-, -NH-, CHF, CF_2, -CH(O-loweralkyl)-, -CH(O-loweracyl)-, $-CH(OSO_3H)-$, $-CH(OPO_3H_2)-$, $-CH(OB(OH)_2)-$, or -NOH-;

with the provisos that

(1) R^{5g} cannot be -CN; 2,5-dimethoxy; 2,6-dimethoxy or halogen when neither of R^4 and R^{5g} includes an -OH, amino, loweralkyl, O-loweralkyl, alkoxycarbonyl, $-B(OH)_2$, $-PO_3H_2$ or $-SO_3H$ group;

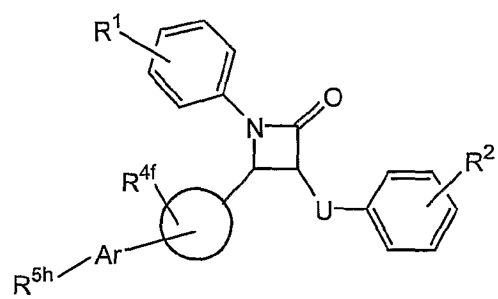
(2) R^{5g} cannot be 2-hydroxy when  represents a 2,5-thienyl residue;

(3) adjacent $-CH_2-$ residues in U^a cannot be replaced by -S-, -S(O)-, $-SO_2-$ or -O- ;

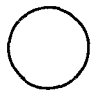
(4) -S-, -S(O)-, $-SO_2-$, -O- and -NH- residues in U^a cannot be separated only by a single carbon; and

(5) U^a cannot be $-CH_2CH_2CH(OH)-$, wherein the left end of the string is the point of attachment to the azetidinone ring and the right end of the string is the point of attachment to the phenyl ring.

3. A compound of formula:



wherein

 represents an aryl or heteroaryl residue;

Ar represents an aryl residue;

R^1 represents one, two, three, four or five residues chosen independently from H, halogen, -OH, loweralkyl, OCF_2H, OCF_3, CF_2H, CH_2F, -O-loweralkyl, methylenedioxy, ethylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -SH, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, alkoxycarbonyl, carboxyalkyl, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy, $-PO_3H_2$, $-SO_3H$, $-B(OH)_2$, a sugar, a polyol, a glucuronide and a sugar carbamate;

R^2 represents one, two, three, four or five residues chosen independently from H, halogen, -OH, loweralkyl, OCF_2H, OCF_3, CF_2H, CH_2F, -O-loweralkyl, methylenedioxy, ethylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -SH, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, alkoxycarbonyl, carboxyalkyl, carboxamido, alkylsulfoxide, acylamino, amidino, $-PO_3H_2$, $-SO_3H$, $-B(OH)_2$, a sugar, a polyol, a glucuronide and a sugar carbamate;

R^{4f} is -OH, -SH or $-B(OH)_2$;

R^{5h} represents one, two, three, four or five residues on Ar chosen independently from hydrogen, halogen, -OH, loweralkyl, -O-loweralkyl, methylenedioxy, ethylenedioxy, hydroxyloweralkyl, -CN, $-CF_3$, nitro, -SH, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, alkoxycarbonyl, carboxyalkyl, carboxamido, alkylsulfoxide, acylamino, amidino, $-PO_3H_2$, $-SO_3H$, $-B(OH)_2$, a sugar, a polyol, a glucuronide and a sugar carbamate;

U is $(C_2\text{-}C_6)$-alkylene in which one or more $-CH_2-$ may be replaced by a radical chosen from -S-, -S(O)-, $-SO_2-$, -O-, -C(=O)-, -CHOH-, -NH-, CHF, CF_2, -CH(O-loweralkyl)-, -CH(O-loweracyl)-, $-CH(OSO_3H)-$, $-CH(OPO_3H_2)-$, $-CH(OB(OH)_2)-$, or -NOH-,

with the provisos that:

(1) adjacent $-CH_2-$ residues in U cannot be replaced by -S-, -S(O)-, $-SO_2-$ or -O- ; and

(2) -S-, -S(O)-, $-SO_2-$, -O- and -NH- residues in U cannot be separated only by a single carbon.

4. A compound according to claim 2 wherein U^a is chosen from $-SCH_2CH_2-$, $-S(O)CH_2CH_2-$, $-S(O)CH_2CH(OH)-$, $-SCH_2C(=O)-$, $-SCH_2CH(OH)-$, $-CH(OH)CH_2CH_2-$, $-CH(OH)CH_2CH(OH)-$, $-(CH_2)_3CH(OH)-$ and $-(CH_2)_4-$, wherein the left end of the string is the point of attachment to the azetidinone ring and the right end of the string is the point of attachment to the phenyl ring.

5. A compound according to claim 1 or 3 wherein U is chosen from $-CH_2CH_2CH(OH)-$, $-SCH_2CH_2-$, $-S(O)CH_2CH_2-$, $-S(O)CH_2CH(OH)-$, $-SCH_2C(=O)-$, $-SCH_2CH(OH)-$, $-CH(OH)CH_2CH_2-$, $-CH(OH)CH_2CH(OH)-$, $-(CH_2)_3CH(OH)-$ and $-(CH_2)_4-$, wherein the left end of the string is the point of attachment to the azetidinone ring and the right end of the string is the point of attachment to the phenyl ring.

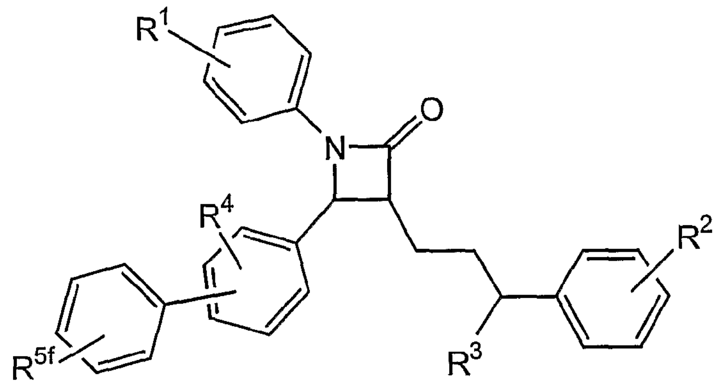
6. A compound according to claim 5 wherein U is $-CH_2CH_2CH(OH)-$.

7. A compound according to any of claims 1-4 wherein
R^1 represents one or two residues;
R^2 represents one or two residues;
R^4 represents one or two residues; and
R^{5g} or R^{5h} represents one or two residues.

8. A compound according to claim 7 wherein
R^1 represents one residue;
R^2 represents one residue;
R^4 represents one residue; and

R^5 represents one residue.

9. A compound of formula:



wherein

R^1 and R^2 represent one or two residues chosen independently from H, halogen, -OH, loweralkyl, OCF_2H, OCF_3, CF_2H, CH_2F, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, hydroxyamidino, guanidino, dialkylguanidino, phenyl, benzyl, phenoxy, benzyloxy, a sugar,.a glucuronide, and a sugar carbamate;

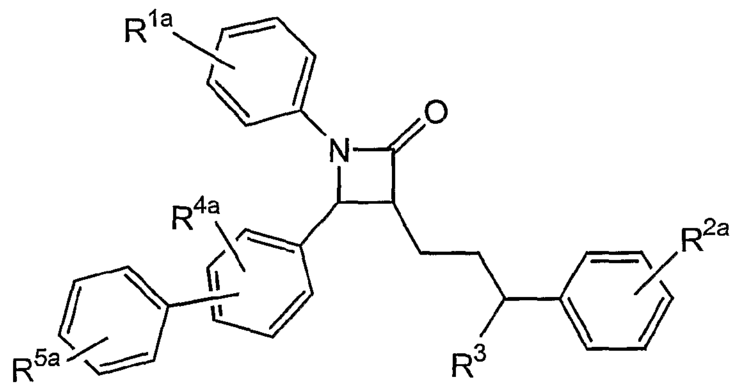
R^3 is chosen from H, -OH, fluoro, -O-loweralkyl and -O-acyl;

R^4 represents one, two, three or four residues chosen independently from H, halogen, -OH, loweralkyl, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy, a sugar, a glucuronide and a sugar carbamate;

R^{5f} represents from one to five residues chosen independently from halogen, -OH, loweralkyl, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy, a sugar, a glucuronide a sugar carbamate and - $N^+R^6R^7R^8\ X^-$;

R^6 is C_1 to C_{20} hydrocarbon or forms a five- to seven-membered ring with R^7;
R^7 is alkyl or forms a five- to seven-membered ring with R^6;
R^8 is alkyl or together with R^6 or R^7 forms a second five- to seven-membered ring;
and
X is an anion.

10. A compound of formula:



wherein

R^{2a} represents one or two residues chosen independently from H, halogen, -OH, loweralkyl, OCF_2H, OCF_3, CF_2H, CH_2F, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy;

R^3 is chosen from H, -OH, fluoro, -O-loweralkyl and -O-acyl;

one of R^{1a}, R^{4a} and R^{5a} is $-Q-A-N^+R^9R^{10}R^{11}\ X^-$

and the other two of R^{1a}, R^{4a} and R^{5a} are chosen independently from hydrogen, halogen, -OH, loweralkyl, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl,

phenoxy, benzyloxy;

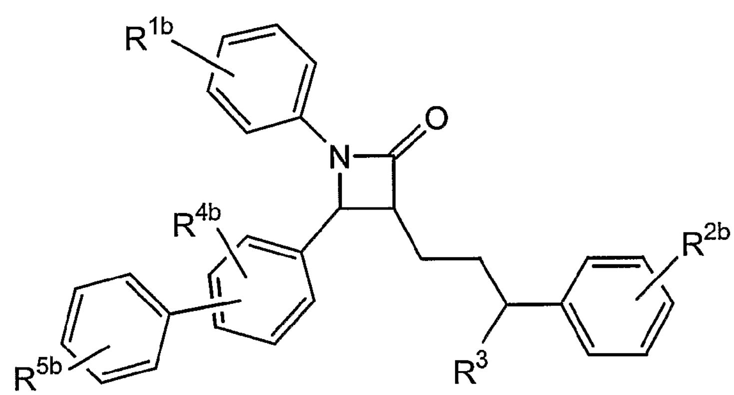
Q is chosen from a direct bond, -O-, -S-, -NH-, $-CH_2O-$, $-CH_2NH-$, -C(=O)-, -CONH-, -NHCO-, $-CH_2NH(C=O)-$, -O(C=O)-, -(C=O)O-, -NHCONH-, -OCONH- and -NHCOO- ;

A is chosen from C_2 to C_{20} hydrocarbon, substituted alkyl of 2 to 20 carbons, substituted aryl, substituted arylalkyl, and oxaalkyl of four to fifty carbons; and, when Q is a direct bond, -C(=O) or –O(C=O)-, A may additionally be methylene;

R^9 is C_1 to C_{20} hydrocarbon or forms a five- to seven-membered ring with A or R^{10};
R^{10} is alkyl, forms a double bond with A or forms a five- to seven-membered ring with R^9;
R^{11} is alkyl or together with R^{10} or R^9 forms a second five- to seven-membered ring; and

X is an anion.

11. A compound of formula:



wherein
R^{2b} represents one or two residues chosen independently from H, halogen, -OH, loweralkyl, OCF_2H, OCF_3, CF_2H, CH_2F, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl,

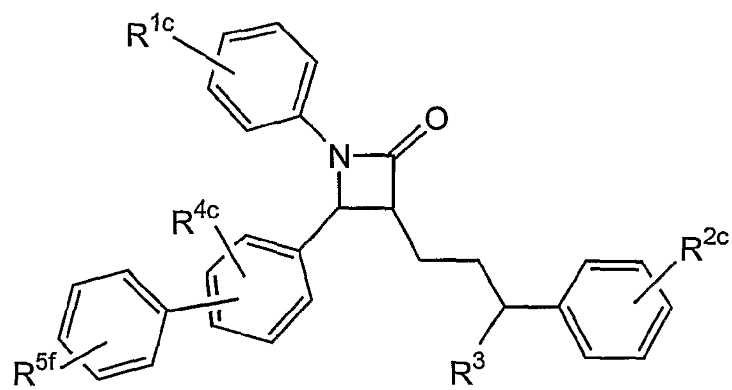
acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy;

R^3 is chosen from H, -OH, fluoro, -O-loweralkyl and -O-acyl;

one of R^{1b}, R^{4b} and R^{5b} is R^{12} and the other two of R^{1b}, R^{4b} and R^{5b} are chosen independently from hydrogen, halogen, -OH, loweralkyl, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy, a sugar, a glucuronide, and a sugar carbamate;

R^{12} is (C_0 to C_{30})alkylene-G_n in which one or more -CH_2- residues in said alkylene may be replaced by -S-, -SO-, SO_2-, -O-, -NH-, -N(alkyl)-, -N(phenyl)-, -N(alkylphenyl)-, -N^+(alkyl)$_2$-, -N^+(phenyl)$_2$-, -N^+(alkylphenyl)$_2$-, -C(=O)-, -C(=S), CH=CH-, -C=C-, phenylene or -N[(C=O)alkyleneCOOH]-;
G is chosen from -SO_3H, -PO_3H_2, -O-PO_3H_2, -COOH, -C(N=H)NH_2, a polyol, a sugar, a glucuronide, a sugar carbamate, -$N^+R^{6a}R^{7a}R^{8a}$ X^-, and a mono or bicyclic trialkylammoniumalkyl residue;
R^{6a} is C_1 to C_{20} hydrocarbon;
R^{7a} is alkyl;
R^{8a} is alkyl;
n is 1, 2, 3, 4 or 5; and
X is an anion.

12. A compound of formula:



wherein

R^{1c} and R^{2c} represent one or two residues chosen independently from H, halogen, -OH, loweralkyl, OCF_2H, OCF_3, CF_2H, CH_2F, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, hydroxyamidino, guanidino, dialkylguanidino, phenyl, benzyl, phenoxy, benzyloxy, a glucuronide, and a sugar carbamate;

R^3 is chosen from H, -OH, fluoro, -O-loweralkyl and -O-acyl;

R^{4c} represents one, two, three or four residues chosen independently from H, halogen, -OH, loweralkyl, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy, a glucuronide and a sugar carbamate;

R^{5f} represents one, two, three, four or five residues chosen independently from halogen, -OH, loweralkyl, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy, a sugar, a glucuronide a sugar carbamate and - $N^+R^6R^7R^8\ X^-$;

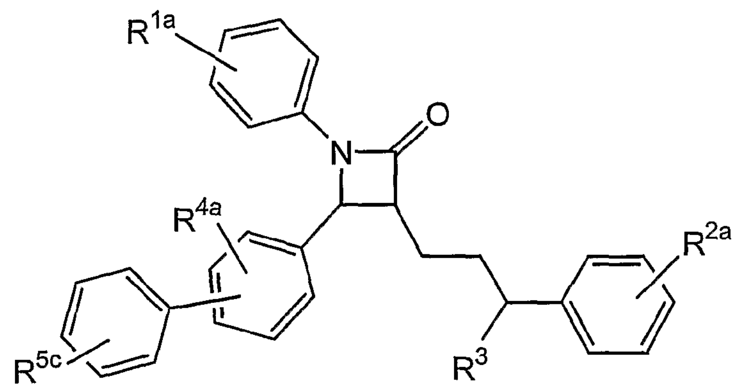
R^6 is C_1 to C_{20} hydrocarbon or forms a five- to seven-membered ring with R^7;

R^7 is alkyl or forms a five- to seven-membered ring with R^6;

R^8 is alkyl or together with R^6 or R^7 forms a second five- to seven-membered ring; and

X is an anion.

13. A compound of formula:



wherein

R^{1a}, R^{2a} and R^{4a} each represents one or two residues chosen independently from H, halogen, -OH, loweralkyl, OCF_2H, OCF_3, CF_2H, CH_2F, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy;

R^3 is chosen from H, -OH, fluoro, -O-loweralkyl and -O-acyl;

R^{5c} is $-Q-A-N^+R^9R^{10}R^{11}\ X^-$;

Q is chosen from a direct bond, -O-, -S-, -NH-, $-CH_2O-$, $-CH_2NH-$, -C(=O)-, -CONH-, -NHCO-, $-CH_2NH(C{=}O)-$, -O(C=O)-, -(C=O)O-, -NHCONH-, -OCONH- and -NHCOO- ;

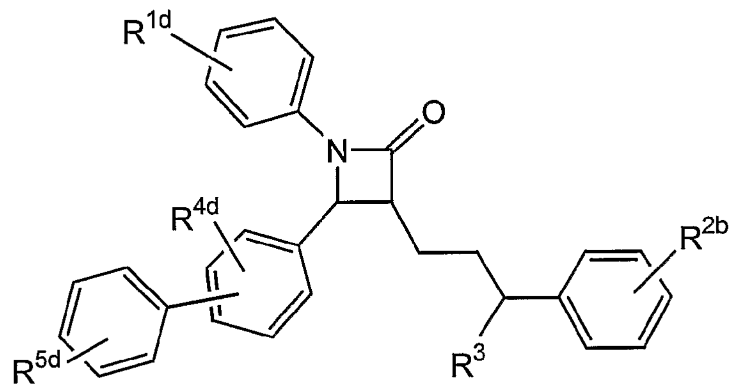
A is chosen from C_2 to C_{20} hydrocarbon, substituted alkyl of 2 to 20 carbons, substituted aryl, substituted arylalkyl, and oxaalkyl of four to fifty carbons; and, when

Q is a direct bond, -C(=O) or –O(C=O)-, A may additionally be methylene;

R^9 is C_1 to C_{20} hydrocarbon or forms a five- to seven-membered ring with A or R^{10};
R^{10} is alkyl, forms a double bond with A or forms a five- to seven-membered ring with R^9;
R^{11} is alkyl or together with R^{10} or R^9 forms a second five- to seven-membered ring; and

X is an anion.

14. A compound of formula:



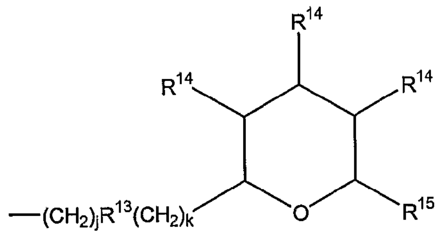
wherein

R^{2b} represents one or two residues chosen independently from H, halogen, -OH, loweralkyl, OCF_2H, OCF_3, CF_2H, CH_2F, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, and benzyloxy;

R^3 is chosen from H, -OH, fluoro, -O-loweralkyl and -O-acyl;

one of R^{1d}, R^{4d} and R^{5d} is R^{12a} and the other two of R^{1d}, R^{4d} and R^{5d} are chosen independently from hydrogen, halogen, -OH, loweralkyl, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino,

alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy and R^{12a};

R^{12a} is 

, or, when R^{5d} is R^{12a}, R^{12a} may additionally be

(C_0 to C_{30})alkylene-G_n in which one or more $-CH_2-$ residues in said alkylene may be replaced by -S-, -SO-, SO_2-, -O-, -NH-, -N(alkyl)-, -N(phenyl)-, -N(alkylphenyl)-, $-N^+(alkyl)_2-$, $-N^+(phenyl)_2-$, $-N^+(alkylphenyl)_2-$, -C(=O)-, -C(=S), CH=CH-, -C≡C-, phenylene or -N[(C=O)alkyleneCOOH]-;

G is chosen from $-SO_3H$, $-PO_3H_2$, $-O-PO_3H_2$, -COOH, $-C(N=H)NH_2$, a polyol, a sugar, a glucuronide, a sugar carbamate, $-N^+R^{6a}R^{7a}R^{8a}\ X^-$, and a mono or bicyclic trialkylammoniumalkyl residue;

R^{6a} is C_1 to C_{20} hydrocarbon;

R^{7a} is alkyl;

R^{8a} is alkyl;

R^{13} is chosen from a direct bond, -C≡C-, $-OCH_2$, -C(=O)- and -CHOH-;

R^{14} is chosen from -OH and -OC(=O)alkyl;

R^{15} is chosen from $-CH_2OH$, $-CH_2OC(=O)$alkyl and -COOalkyl;

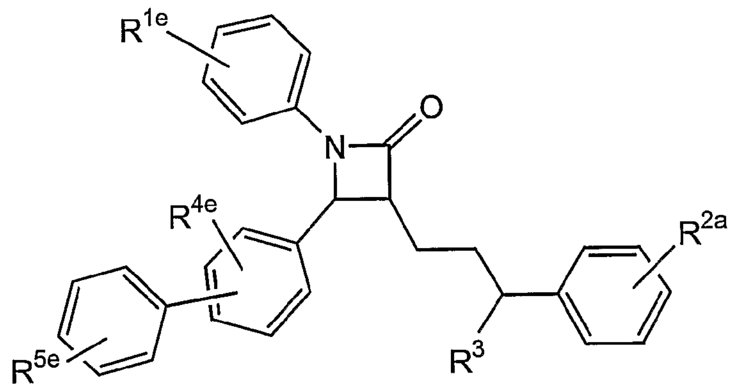
j is 1, 2, 3, 4 or 5;

k is zero, 1, 2, 3, 4 or 5;

n is 1, 2, 3, 4 or 5; and

X is an anion.

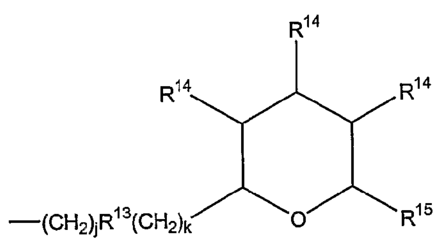
15. A compound of formula:



wherein

R^{1e}, R^{2a} and R^{4e} each represents one or two residues chosen independently from H, halogen, -OH, loweralkyl, OCF_2H, OCF_3, CF_2H, CH_2F, -O-loweralkyl, methylenedioxy, hydroxyloweralkyl, -CN, CF_3, nitro, -S-loweralkyl, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, acyl, carboxy, carboalkoxy, carboxamido, alkylsulfoxide, acylamino, amidino, phenyl, benzyl, phenoxy, benzyloxy;

R^3 is chosen from H, -OH, fluoro, -O-loweralkyl and -O-acyl;

R^{5e} is chosen from  and (C_0 to C_{30})alkylene-G_n in which one or more $-CH_2-$ residues in said alkylene may be replaced by -S-, -SO-, SO_2, -O-, -NH-, -N(alkyl)-, -N(phenyl)-, -N(alkylphenyl)-, $-N^+(alkyl)_2-$, $-N^+(phenyl)_2-$, $-N^+(alkylphenyl)_2-$, -C(=O)-, -C(=S), CH=CH-, -C=C-, phenylene or -N[(C=O)alkyleneCOOH]-;

G is chosen from $-SO_3H$, $-P(O)OH_2$, $-OP(O)OH_2$, -COOH, $-C(N{=}H)NH_2$, a polyol, a sugar, a glucuronide, a sugar carbamate, $-N^+R^{6a}R^{7a}R^{8a}\ X^-$, and a mono or bicyclic trialkylammoniumalkyl residue;

R^{6a} is C_1 to C_{20} hydrocarbon;

R^{7a} is alkyl;

R^{8a} is alkyl;

R^{13} is chosen from a direct bond, -C=C-, -OCH_2, -C(=O)- and -CHOH-;

R^{14} is chosen from -OH and -OC(=O)alkyl;

R^{15} is chosen from -CH_2OH, -CH_2OC(=O)alkyl and -COOalkyl;

j is 1, 2, 3, 4 or 5;

k is zero, 1, 2, 3, 4 or 5; and

X is an anion.

16. A compound according to any of claims 1, 2, 4 or 9-15 wherein R^1, R^2 and R^4 are chosen from H, halogen, -OH, and methoxy.

17. A compound according to any of claims 1-4, 9, 11 or 15 wherein at least one of R^1, R^2, R^4 and R^5 is chosen from a sugar, a glucuronide and a sugar carbamate.

18. A compound according to any of claims 1-4, 9, 11 or 15 wherein at least one of R^1, R^2, R^4 and R^5 is chosen from SO_3H and PO_3H_2.

19. A compound according to any of claims 9-15 wherein R^3 is chosen from hydrogen and hydroxy.

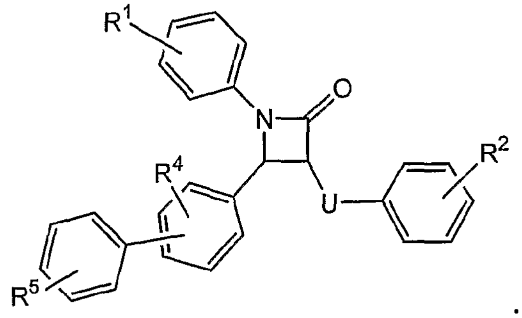
20. A compound according to any of claims 1, 2, 4 or 9-15 wherein R^4 is hydrogen.

21. A compound according to any of claims 1, 2, 4 or 9-15 wherein R^4 is OH.

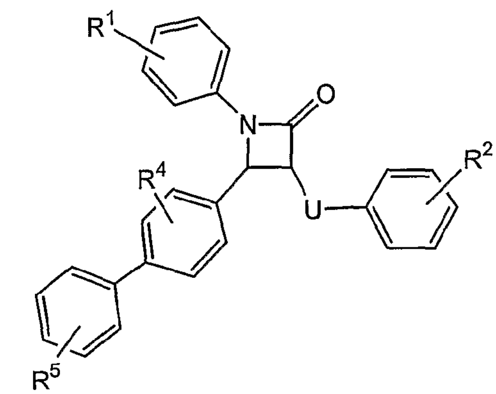
22. A compound according to any of claims 1-4 or 9-15 wherein R^5 is chosen from halogen, hydroxy, loweralkyl, -O-loweralkyl, CF_3, alkylsulfonyl, arylsulfonyl, hydroxymethyl, formyl, cyano, N,N-dimethylsulfonamido, carboxy, nitro, acetamido, dialkylamino, methylthio, vinyl, methylenedioxy, ethylenedioxy, carboxymethyl,

$-PO_3H_2$, mercapto, $-SO_3H$, $-B(OH)_2$, a trialkylammonium cation, a sugar and a glucuronide.

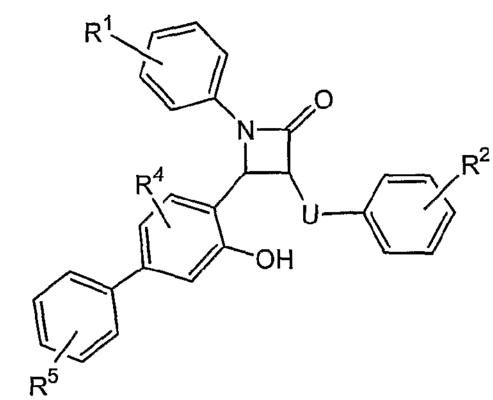
23. A compound according to any of claims 1, 2 or 3 of formula



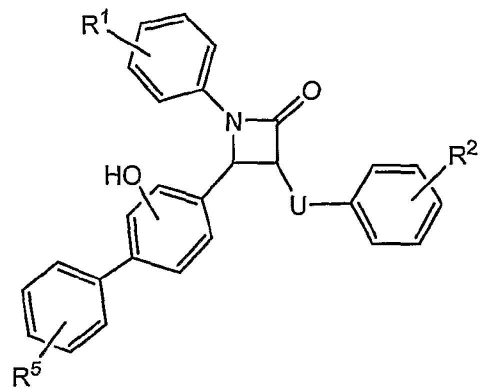
24. A compound according to claim 23 of formula



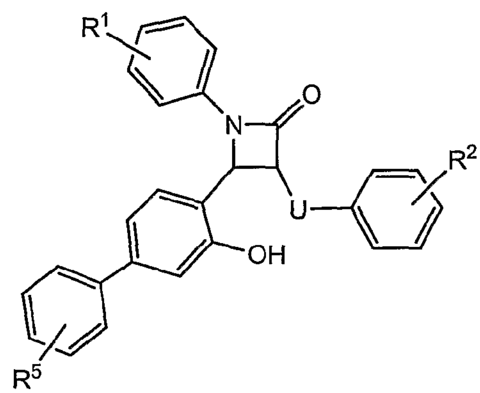
25. A compound according to claim 24 of formula



26. A compound according to claim 24 of formula

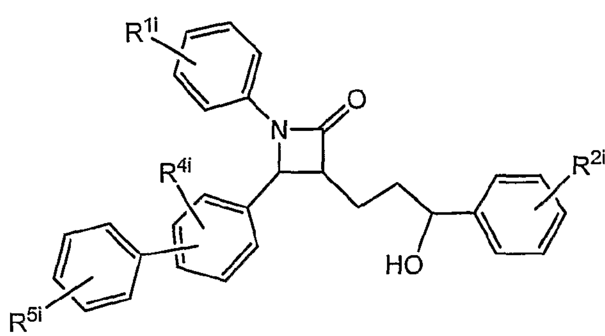


27. A compound according to claim 26 of formula



28. A compound according to claim 27 wherein R^1 is H.

29. A compound of formula



wherein

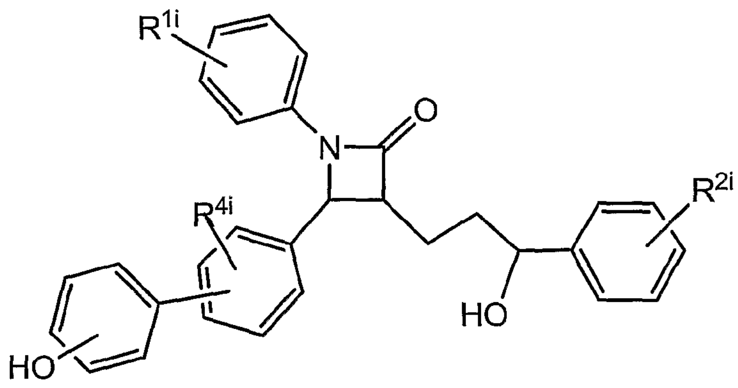
R^{1i} and R^{2i} are independently chosen from H, F, Cl, CH_3, CN, OCH_3, OCF_3, OCF_2H,

CF_3, CF_2H, and CH_2F;

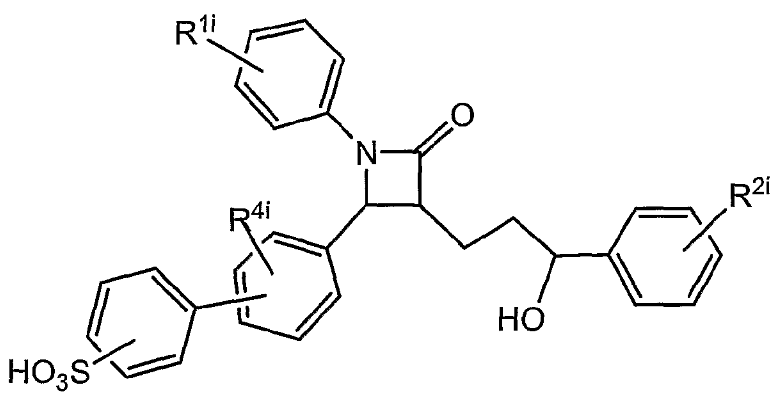
R^{4i} is chosen from H, F, Cl, CH_3, OCH_3, OH, $B(OH)_2$, and SH; and

R^{5i} is chosen from OH, SO_3H, PO_3H_2, CH_2OH, COOH, CHO and a sugar.

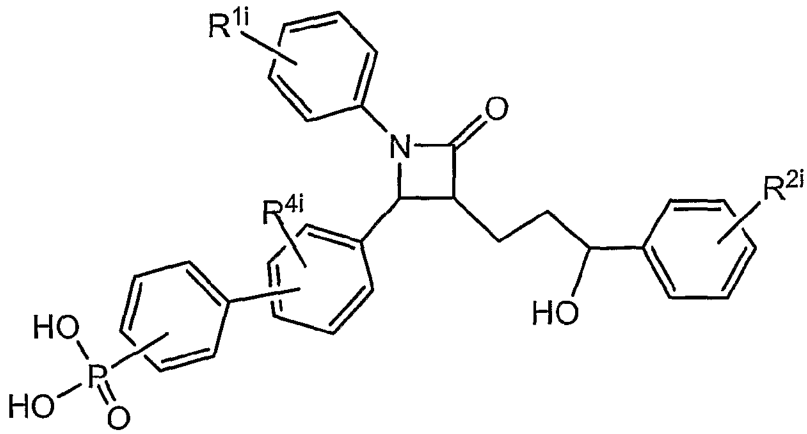
30. A compound according to claim 29 wherein R^{5i} is -OH of formula



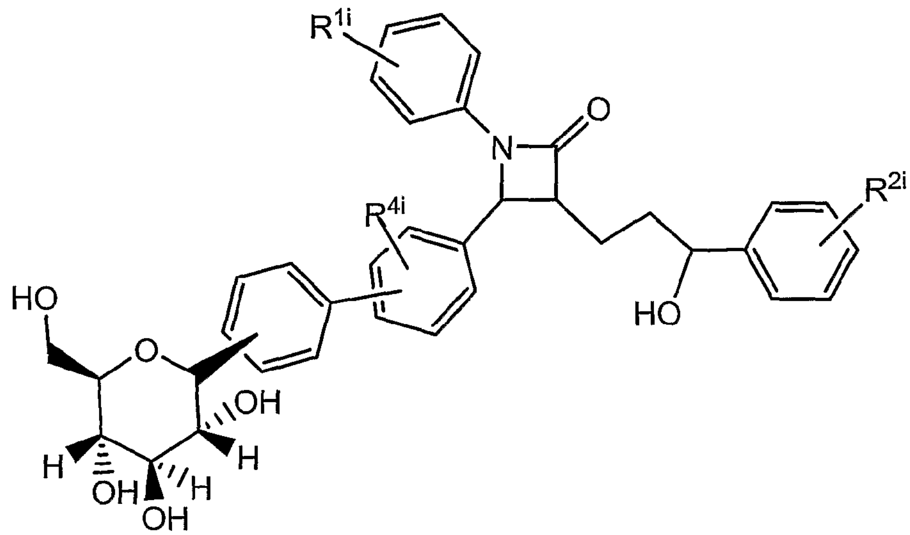
31. A compound according to claim 29 wherein R^{5i} is $-SO_3H$ of formula



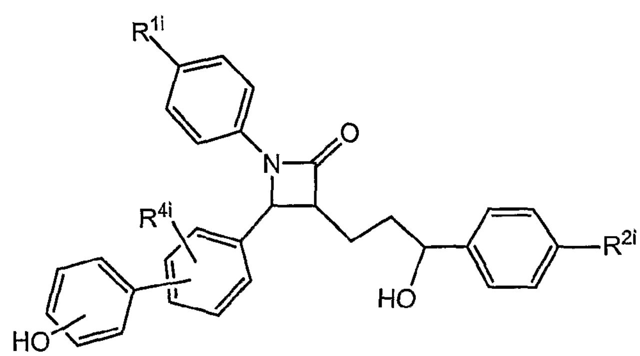
32. A compound according to claim 29 wherein R^{5i} is $-PO_3H_2$ of formula



33. A compound according to claim 29 wherein R^{5i} is D-glucitol of formula

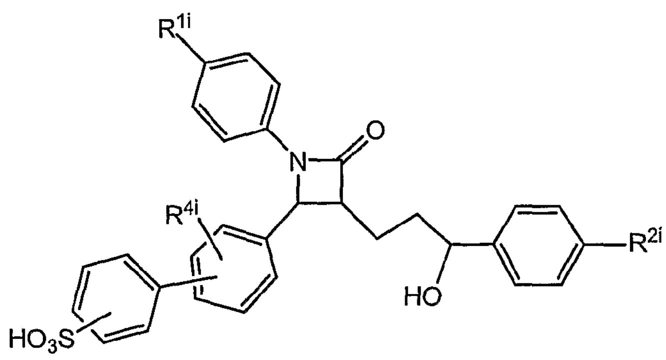


34. A compound according to claim 30 wherein R^{5i} is -OH of formula

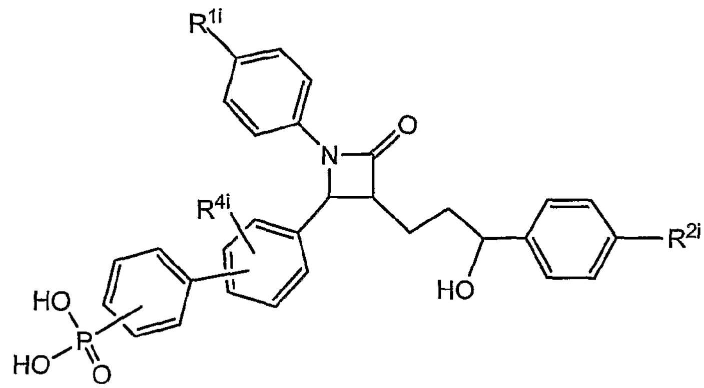


.

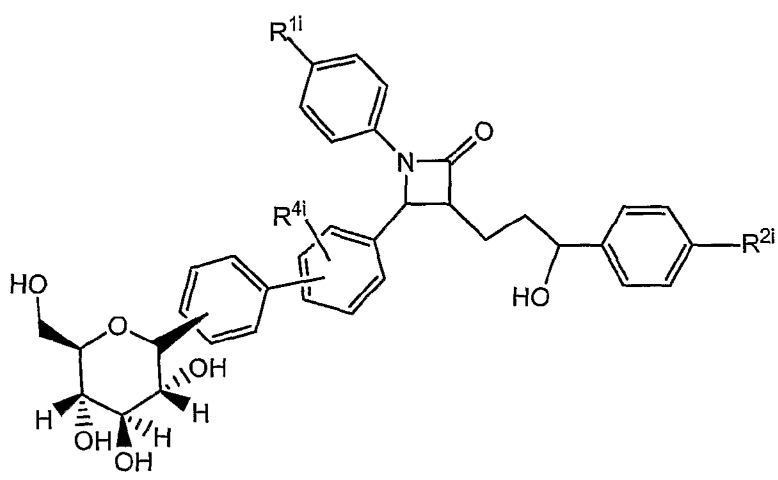
35. A compound according to claim 31 wherein R^{5i} is $-SO_3H$ of formula



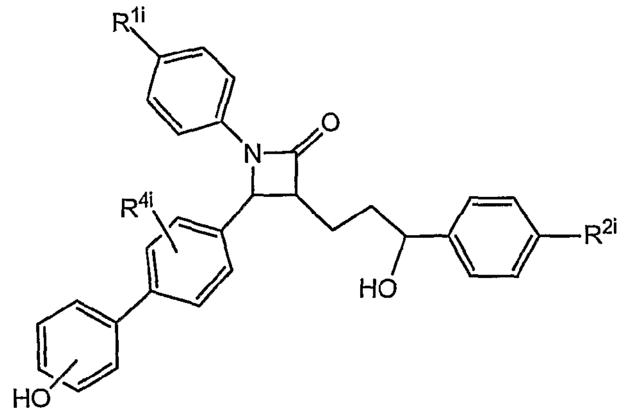
36. A compound according to claim 32 wherein R^{5i} is $-PO_3H_2$ of formula



37. A compound according to claim 33 wherein R^{5i} is D-glucitol of formula

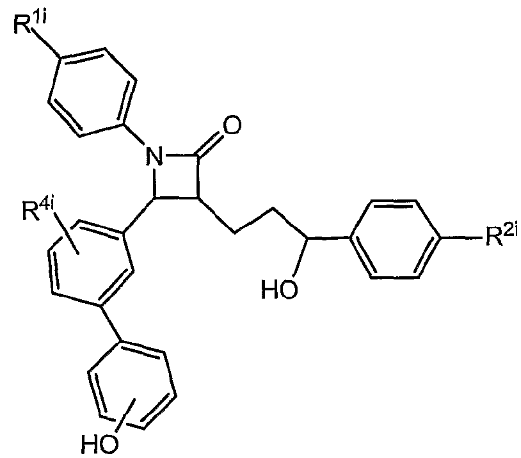


38. A compound according to claim 34 wherein R^{5i} is -OH of formula



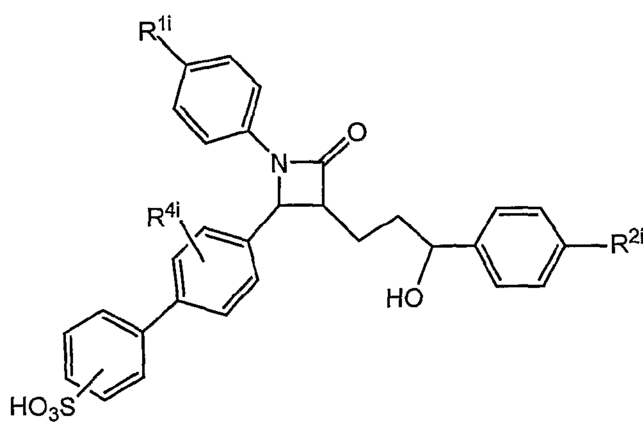
.

39. A compound according to claim 34 wherein R^{5i} is -OH of formula



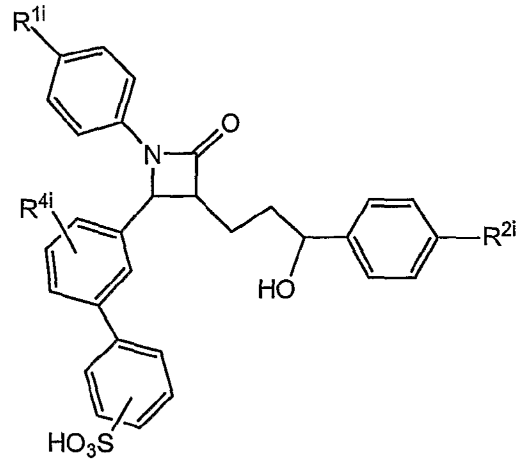
.

40. A compound according to claim 35 wherein R^{5i} is $-SO_3H$ of formula

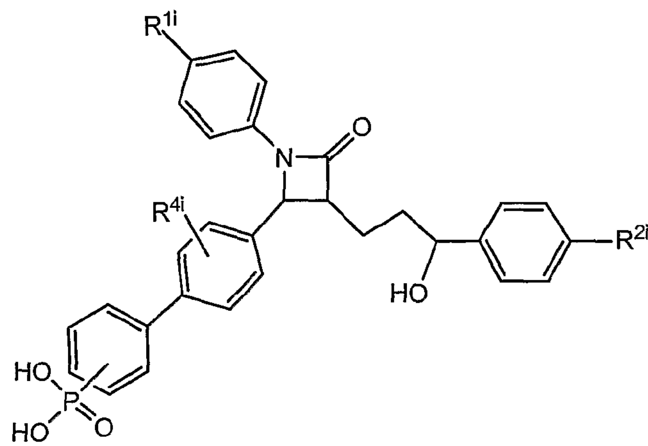


.

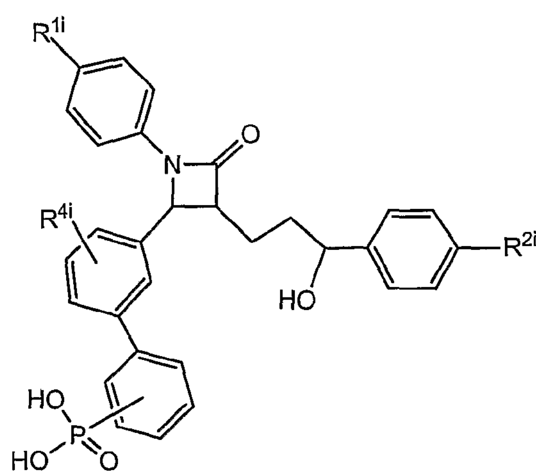
41. A compound according to claim 35 wherein R^{5i} is $-SO_3H$ of formula



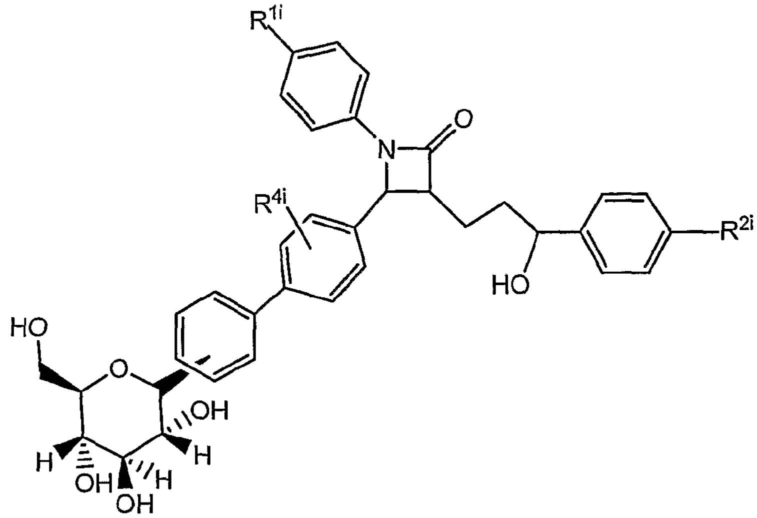
42. A compound according to claim 36 wherein R^{5i} is $-PO_3H_2$ of formula



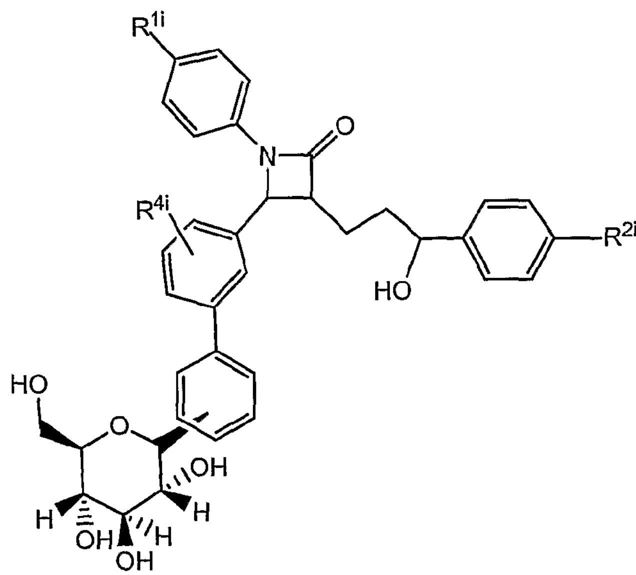
43. A compound according to claim 36 wherein R^{5i} is $-PO_3H_2$ of formula



44. A compound according to claim 37 wherein R^{5i} is D-glucitol of formula



45. A compound according to claim 37 wherein R^{5i} is D-glucitol of formula



46. A compound according to any of claims 29-45 wherein R^{4i} is OH.

47. A compound according to claim 46 wherein R^{4i} is ortho to the azetidine ring.

48. A compound according to any of claims 29-45 wherein R^{5i} is an ortho substituent.

49. A compound according to any of claims 29-45 wherein R^{5i} is a meta substituent.

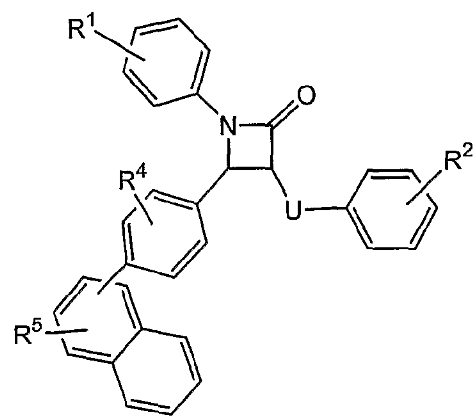
50. A compound according to any of claims 29-45 wherein R^{5i} is a para substituent.

51. A compound according to any of claims 29-45 wherein R^{1i} and R^{2i} are chosen from H, Cl and F.

52. A compound according to claim 51 wherein R^{1i} is H.

53. A compound according to claim 29 wherein said sugar is D-glucitol

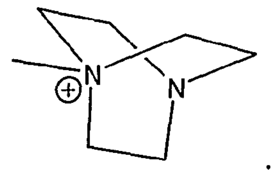
54. A compound according to any of claims 1-4 of formula



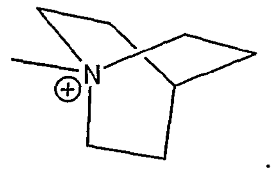
55. A compound according to any of claims 1, 2, 3, or 29 wherein
R^1 is H or 4-fluoro;
R^2 is 4-fluoro; and
R^4 is H or hydroxy.

56. A compound according to claim 10 or 13 wherein one of R^1, R^4 and R^5 is -Q-A-N^+ $R^9R^{10}R^{11}$ X^- -Q-A- is chosen from (C_2 to C_{20} hydrocarbon), -O-(C_2 to C_{20} hydrocarbon), -NH(C_2 to C_{20} hydrocarbon), -NHCO(C_2 to C_{20} hydrocarbon) and oxaalkyl of four to twenty carbons; R^9 is loweralkyl or benzyl and R^{10} and R^{11} are loweralkyl, or

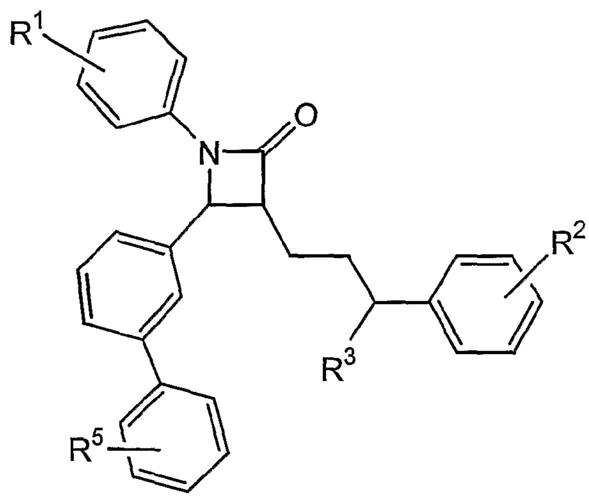
R^9, R^{10} and R^{11} taken together form a diazabicyclooctane quat:



or R^9,R^{10} and R^{11} taken together form a quinuclidinium quat:



57. A compound according to any of claims 1, 2, 9 or 12 of formula



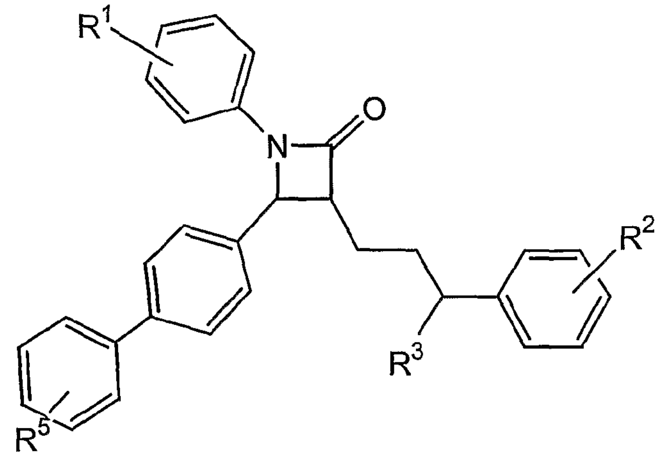
wherein

R^1 and R^2 are chosen from H, halogen, -OH, and methoxy;

R^3 is chosen from hydrogen and hydroxy; and

R^5 is chosen from halogen, hydroxy, loweralkyl, -O-loweralkyl, CF_3, alkylsulfonyl and arylsulfonyl.

58. A compound according to any of claims 1, 2, 9 or 12 of formula



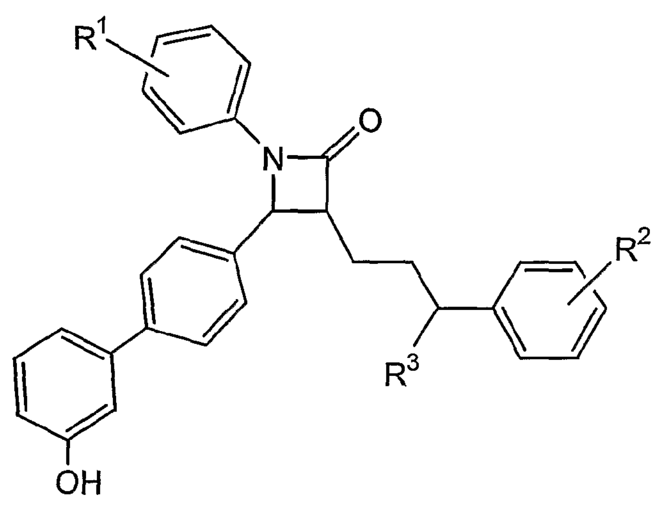
wherein

R^1 and R^2 are chosen from H, halogen, -OH, and methoxy;

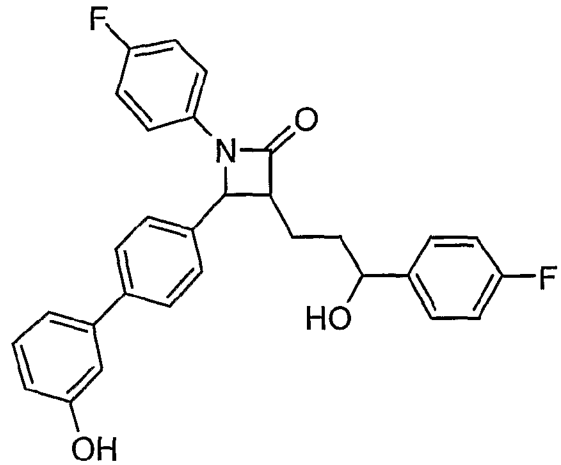
R^3 is chosen from hydrogen and hydroxy; and

R^5 is chosen from halogen, hydroxy, loweralkyl, -O-loweralkyl, CF_3, alkylsulfonyl and arylsulfonyl.

59. A compound according to claim 58 of formula



60. A compound according to claim 59 of formula



61. A compound according to claim 11 wherein

R^{1b} is R^{12} ;

R^{2b} and R^{4b} are chosen from H, halogen, -OH, and methoxy;

R^{12} is (C_6 to C_{20})alkylene-G in which one or more $-CH_2-$ residues in said alkylene may be replaced by -O-, -NH-, -N(alkyl)-, -C(=O)- or -CH=CH-; and

G is chosen from $-SO_3H$, $-PO_3H_2$, a polyol, and a sugar.

62. A compound according to any of claims 11, 14 or 15 wherein

R^5 is R^{12} ;

R^1, R^2 and R^4 are chosen from H, halogen, -OH, and methoxy;

R^{12} is (C_6 to C_{20})alkylene-G in which one or more $-CH_2-$ residues in said alkylene may be replaced by -O-, -NH-, -N(alkyl)-, -C(=O)- or -CH=CH-; and

G is chosen from $-SO_3H$, $-PO_3H_2$, a polyol, and a sugar.

63. A compound according to any of claims 1-4, 8-15 and 29-45 wherein the substituents at positions 3 and 4 of the azetidin-2-one are in a cis relative configuration.

64. A compound according to any of claims 1-4, 8-15 and 29-45 wherein the substituents at positions 3 and 4 of the azetidin-2-one are in a trans relative configuration.

65. A compound according to claim 64 wherein the substituent at position 3 of the azetidin-2-one is of the R absolute configuration and the substituent at position 4 of the azetidin-2-one is of the S absolute configuration.

66. A compound according to any of claims 1-3 wherein U is (C_2-C_6)-alkylene in which at least one -CH_2- is replaced by -CHOH-.

67. A compound chosen from the group consisting of:

(1) (1R)-1,5-anhydro-1-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-4-yl)-L-glucitol,
(2) (1S)-1,5-anhydro-1-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)-L-glucitol,
(3) (1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucitol,
(4) (1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol,
(5) (1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)-D-glucitol,
(6) (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(2',3',4'-trimethoxybiphenyl-4-yl)azetidin-2-one,
(7) (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-hydroxybiphenyl-4-yl)azetidin-2-one,
(8) (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-mercaptobiphenyl-4-yl)azetidin-2-one,
(9) (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-methoxybiphenyl-4-yl)azetidin-2-one,

(10) (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-nitrobiphenyl-4-yl)azetidin-2-one,

(11) (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4'-hydroxy-3'-methoxybiphenyl-4-yl)azetidin-2-one,

(12) (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4'-vinylbiphenyl-4-yl)azetidin-2-one,

(13) (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[3'-(hydroxymethyl)biphenyl-4-yl]azetidin-2-one,

(14) (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[3'-(methylsulfonyl)biphenyl-4-yl]azetidin-2-one,

(15) (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[4-(2-naphthyl)phenyl]azetidin-2-one,

(16) (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[4'-(hydroxymethyl)biphenyl-4-yl]azetidin-2-one,

(17) (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[4'-(methylsulfonyl)biphenyl-4-yl]azetidin-2-one,

(18) (3R,4S)-1-biphenyl-4-yl-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-hydroxybiphenyl-4-yl)azetidin-2-one,

(19) (3R,4S)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(3'-hydroxybiphenyl-4-yl)-1-phenylazetidin-2-one,

(20) (3R,4S)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[3-hydroxy-3'-(methylsulfonyl)biphenyl-4-yl]-1-phenylazetidin-2-one,

(21) (3R,4S)-4-(2',3'-difluorobiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one,

(22) (3R,4S)-4-(2',4'-dihydroxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one,

(23) (3R,4S)-4-(2'-bromo-5'-hydroxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one,

(24) (3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one,

(25) (3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-

hydroxypropyl]-1-phenylazetidin-2-one,

(26) (3R,4S)-4-(3,4'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one,

(27) (3R,4S)-4-(3',5'-dihydroxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one,

(28) (3R,4S)-4-(3',5'-dimethoxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one,

(29) (3R,4S)-4-(3'-butoxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one,

(30) (3R,4S)-4-(3'-ethoxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one,

(31) (3R,4S)-4-(3'-fluoro-5'-hydroxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one,

(32) (3R,4S)-4-(3'-fluoro-5'-methoxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one,

(33) (3R,4S)-4-(4'-aminobiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one,

(34) (3R,4S)-4-(4'-ethoxybiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one,

(35) (3R,4S)-4-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one,

(36) (3R,4S)-4-[4'-(dimethylamino)biphenyl-4-yl]-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one,

(37) (4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)boronic acid,

(38) (4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)phosphonic acid,

(39) (4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)phosphonic acid,

(40) (4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)boronic acid,

(41) (4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)phosphonic acid,
(42) (6R)-6-C-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucopyranose,
(43) (6R)-6-C-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)-D-glucopyranose,
(44) (6S)-6-C-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucitol,
(45) (6S)-6-C-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucopyranose,
(46) (6S)-6-C-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}biphenyl-3-yl)-D-glucopyranose,
(47) 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-3-hydroxybiphenyl-4-carboxylic acid,
(48) 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-4-hydroxybiphenyl-3-carboxylic acid,
(49) 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-5-hydroxybiphenyl-2-carbaldehyde,
(50) 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-carbaldehyde,
(51) 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-carboxylic acid,
(52) 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-sulfonic acid,
(53) 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl β-L-glucopyranoside,
(54) 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl β-L-glucopyranosiduronic acid,
(55) 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-4-carboxylic acid,
(56) 4'-{(2S,3R)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-

yl}-3'-hydroxybiphenyl-3-sulfonic acid,

(57) 6-O-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)-D-glucitol,

(58) 6-O-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)-D-glucopyranose,

(59) methyl 4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-4-carboxylate,

(60) methyl 6-O-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)-a-D-glucopyranoside,

(61) N-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)acetamide,

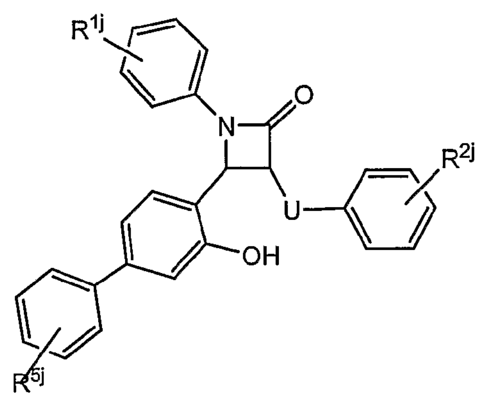
(62) (4'-{(2S,3R)-3-[(3S)-3-(4-Fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid,

(63) 4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-sulfonic acid; and

(64) sodium 4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-sulfonate.

68. A compound according to any of claims 9-15 wherein X is a pharmaceutically acceptable anion.

69. A compound of formula



wherein

U is (C_2-C_6)-alkylene in which one or more $-CH_2-$ may be replaced by a radical chosen from -S-, -S(O)-, $-SO_2-$, -O-, -C(=O)-, -CHOH-, -NH-, CHF, CF_2, -CH(O-loweralkyl)-, -CH(O-loweracyl)-, $-CH(OSO_3H)-$, $-CH(OPO_3H_2)-$, $-CH(OB(OH)_2)-$, or -NOH-;

R^{1j} and R^{2j} are independently chosen from H, F and Cl; and

R^{5j} is chosen from SO_3H, PO_3H_2, a sugar and a gluconuride.

70. A compound according to claim 69 wherein R^{1j} is H.

71. A compound according to claim 69 wherein R^{2j} is F.

72. A pharmaceutical formulation comprising a compound according to any of claims 1-71 and a pharmaceutically acceptable carrier.

73. A pharmaceutical formulation according to claim 72 additionally comprising a dyslipidemic agent.

74. A pharmaceutical formulation according to claim 73 wherein said dyslipidemic agent is an HMG-CoA reductase inhibitor.

75. A pharmaceutical formulation according to claim 74 wherein said HMG-CoA reductase inhibitor is chosen from the group consisting of atorvastatin, atorvastatin calcium, dihydrocompactin, bervastatin, carvastatin, cerivastatin, crilvastatin, dalvastatin, fluvastatin, glenvastatin, fluindostatin, velostatin, lovastatin, mevastatin, compactin, pitavastatin, pravastatin, rivastatin, rosuvastatin, rosuvastatin calcium, simvastatin, sirrivastatin, and CI-981.

76. A pharmaceutical formulation according to claim 74 wherein said HMG-CoA reductase inhibitor is chosen from the group consisting of atorvastatin and atorvastatin calcium.

77. A pharmaceutical formulation according to claim 74 wherein said HMG-CoA reductase inhibitor is chosen from the group consisting of rosuvastatin and rosuvastatin calcium.

78. A pharmaceutical formulation according to claim 72 additionally comprising at least one bile acid sequestrant.

79. A pharmaceutical formulation according to claim 78 wherein the at least one bile acid sequestrant is selected from the group consisting of cholestyramine, colestipol, colesevelam hydrochloride and mixtures thereof.

80. A pharmaceutical formulation according to claim 72 additionally comprising at least one nicotinic acid or derivative thereof selected from the group consisting of nicotinic acid, niceritrol, nicofuranose, acipimox and mixtures thereof.

81. A pharmaceutical formulation according to claim 72 additionally comprising at least one PPARα agonist.

82. A pharmaceutical formulation according to claim 81 wherein said PPARα agonist is a fibric acid derivative.

83. A pharmaceutical formulation according to claim 82 wherein said fibric acid derivative is selected from the group consisting of fenofibrate, clofibrate, gemfibrozil, ciprofibrate, bezafibrate, clinofibrate, binifibrate, lifibrol and mixtures thereof.

84. A pharmaceutical formulation according to claim 82 wherein said fibric acid derivative is fenofibrate.

85. A pharmaceutical formulation according to claim 82 wherein said fibric acid derivative is Tricor®.

86. A pharmaceutical formulation according to claim 72 additionally comprising at least one cholesterol ester transfer protein (CETP) inhibitor.

87. A pharmaceutical formulation according to claim 86 wherein the least one cholesterol ester transfer protein (CETP) inhibitor is torcetrapib.

88. A pharmaceutical formulation according to claim 86 wherein the least one cholesterol ester transfer protein (CETP) inhibitor is JTT-705.

89. A pharmaceutical formulation according to claim 72 additionally comprising at least one anti-obesity agent.

90. A pharmaceutical formulation according to claim 72 additionally comprising at least one acylcoenzyme A:cholesterol acyltransferase (ACAT) inhibitor.

91. A pharmaceutical formulation according to claim 72 additionally comprising at least one anti-diabetic agent.

92. A pharmaceutical formulation according to claim 91 wherein the at least one anti-diabetic agent is a PPARγ agonist.

93. A pharmaceutical formulation according to claim 92 wherein the PPARγ agonist is selected from the group consisting of rosiglitazone, pioglitazone and ciglitazone.

94. A pharmaceutical formulation according to claim 91 wherein the at least one anti-diabetic agent agent is an agent that decreases endogenous hepatic glucose production.

95. A pharmaceutical formulation according to claim 94 wherein the agent is metformin or phenformin.

96. A pharmaceutical formulation according to claim 91 wherein the at least one anti-diabetic agent agent is an agent that increases insulin release from the pancreas.

97. A pharmaceutical formulation according to claim 96 wherein the agent is selected from carbutamide, tolbutamide, acetohexamide, tolazamide, chlorpropamide, glyburide [glibenclamide], glipizide and gliclazide.

98. A pharmaceutical formulation according to claim 72 additionally comprising at least one antioxidant.

99. A pharmaceutical formulation according to claim 98 wherein the antioxidant is probucol or AGI-1067.

100. A pharmaceutical formulation according to claim 99 wherein the antioxidant is AGI-1067.

101. An article of manufacture comprising a container, instructions, and a pharmaceutical formulation according to claim 72, wherein the instructions are for the administration of the pharmaceutical formulation for a purpose chosen from: treating a condition for which a cholesterol absorption inhibitor is indicated; preventing or treating a cholesterol related disease; inhibiting the absorption of or reducing plasma or tissue concentration of one or more sterols or stanols; preventing or treating sistoserolemia; preventing or treating vascular diseases/disorders and conditions, dyslipidemia, mixed dyslipidemia, hypo α-lipoproteinemia, LDL pattern B, LDL pattern A, primary dysbetalipoproteinemia (Frederickson Type III), hyperlipidemia (including but not limited to hypercholesterolemia, hypertriglyceridemia, sitosterolemia), hypertension, angina pectoris, cardiac arrhythmias, congestive heart failure, and stroke; reducing the incidence of cardiovascular disease-related events; preventing or treating vascular conditions and associated thrombotic events; preventing or treating vascular inflammation; reducing blood plasma or serum concentrations of C-reactive protein; preventing, treating, or ameliorating symptoms of Alzheimer's Disease (AD); regulating production or levels of at least one amyloid β (Aβ) peptide; regulating the amount of ApoE isoform 4 in the bloodstream and/or brain; preventing or treating cognitive related disorders (including dementia); preventing or treating obesity; preventing or decreasing the incidence of xanthomas; preventing or minimizing muscular degeneration and related side effects associated with certain HMG-CoA reductase inhibitors (statins); preventing or treating diabetes and associated conditions; preventing or treating at least one autoimmune disorder; preventing or treating demyelination and associated disorders; preventing or treating cholesterol associated tumors; inhibiting the expression of at least one multiple

("multi")-drug resistance gene or protein in an animal cell; enhancing the effectiveness of a chemotherapeutic agent in a subject having cancer; reversing a multi-drug resistance phenotype exhibited by an animal cell; modulating lipid raft structure; treating or preventing a diseasee associated with lipid raft structure; and preventing or treating osteopenia disorders (bone loss disorders).

102. A pharmaceutical formulation according to claim 72 for the prevention or treatment of a cholesterol-associated tumor additionally comprising at least one other anti-cancer agent.

103. A pharmaceutical formulation according to claim 102 wherein at least one other anti-cancer agent is selected from the group consisting of a steroidal antiandrogen, a non- steroidal antiandrogen, an estrogen, diethylstilbestrol, a conjugated estrogen, a selective estrogen receptor modulator (SERM), a taxane, and a LHRH analog.

104. A pharmaceutical formulation according to claim 103 wherein the non-steroidal antiandrogen is selected from the group consisting of finasteride, flutamide, bicalutamide and nilutamide.

105. A pharmaceutical formulation according to claim 103 wherein the SERM is selected from the group consisting of tamoxifen, raloxifene, droloxifene and idoxifene.

106. A pharmaceutical formulation according to claim 103 wherein the taxane is selected from the group consisting of paclitaxel and docetaxel.

107. A pharmaceutical formulation according to claim 103 wherein the LHRH analog is selected from the group consisting of goserelin acetate and leuprolide acetate.

108. A pharmaceutical formulation according to claim 72 additionally comprising at least one anti-hypertensive compound.

109. A pharmaceutical formulation according to claim 108 wherein said anti-hypertensive compound is a thiazide derivative.

110. A pharmaceutical formulation according to claim 109 wherein said thiazide derivative is selected from the group consisting of hydrochlorothiazide, chlorothiazide and polythiazide.

111. A pharmaceutical formulation according to claim 108 wherein said anti-hypertensive compound is a ß-adrenergic blocker.

112. A pharmaceutical formulation according to claim 111 wherein said ß-adrenergic blocker is selected from the group consisting of atenolol, metoprolol, propranolol, timolol, carvedilol, nadolol and bisoprolol.

113. A pharmaceutical formulation according to claim 108 wherein said antihypertensive compound is a calcium-channel blocker.

114. A pharmaceutical formulation according to claim 113 wherein said calcium-channel blocker is selected from the group consisting of isradipine, verapamil,

nitrendipine, amlodipine, nifedipine, nicardipine, isradipine, felodipine, nisoldipine and diltiazem.

115. A pharmaceutical formulation according to claim 108 wherein said anti-hypertensive compound is an angiotensin-converting-enzyme (ACE) inhibitor.

116. A pharmaceutical formulation according to claim 115 wherein said angiotensin-converting-enzyme (ACE) inhibitor is selected from the group consisting of delapril, captopril, enalopril, lisinopril, quinapril, perindopril, benazepril, trandolapril, fosinopril, ramipril and ceranapril.

117. A pharmaceutical formulation according to claim 108 wherein said anti-hypertensive compound is an angiotensin II receptor antagonist.

118. A pharmaceutical formulation according to claim 117 wherein said angiotensin II receptor antagonist is selected from the group consisting of candesartan, irbesartan, olmesartan, telmisartan and aprosartan.

119. A method for treating a vascular disease and associated condition comprising administering to a mammal a therapeutically effective amount of a compound according to any of claims 1-71.

120. A method according to claim 119, wherein said vascular disease and associated condition is hyperlipidemia.

121. A method according to claim 119, wherein said vascular disease and associated condition is arteriosclerosis.

122. A method according to claim 119, wherein said vascular disease and associated condition is sitosterolemia.

123. A method for inhibiting the absorption of cholesterol from the intestine of a mammal, which comprises administering an effective cholesterol-absorption-inhibiting amount of a compound according to any of claims 1-71 to the mammal.

124. A method of reducing plasma or tissue concentration of at least one non-cholesterol sterol or 5α-stanol comprising administering to a mammal in need of such treatment an effective amount of a compound according to any of claims 1-71.

125. A method for reducing the blood plasma or serum concentrations of LDL cholesterol in a mammal, which comprises administering an effective cholesterol reducing amount of a compound according to any of claims 1-71 to the mammal.

126. A method for reducing the concentrations of cholesterol and cholesterol ester in the blood plasma or serum of a mammal, which comprises administering an effective cholesterol and cholesterol ester reducing amount of a compound according to any of claims 1-71 to the mammal.

127. A method for increasing the fecal excretion of cholesterol in a mammal, which comprises administering an effective cholesterol fecal excretion increasing amount of a compound according to any of claims 1-71 to the mammal.

128. A method for the prophylaxis or treatment of a clinical condition in a mammal, for which a cholesterol absorption inhibitor is indicated, which comprises

administering a therapeutically effective amount of a compound according to any of claims 1-71 to the mammal.

129. A method for reducing the incidence of cardiovascular disease-related events in a mammal, which comprises administering an effective cardiovascular disease-related events reducing amount of a compound according to any of claims 1-71 to the mammal.

130. A method for reducing blood plasma or serum concentrations of C-reactive protein (CRP) in a mammal, which comprises administering a therapeutically effective amount of a compound according to any of claims 1-71 to the mammal.

131. A method for treating or preventing vascular inflammation in a subject comprising administering a compound according to any of claims 1-71 to a subject having a level of C-reactive protein that indicates the presence of vascular inflammation or the potential for vascular inflammation.

132. A method for reducing blood plasma or serum concentrations of triglycerides in a mammal, which comprises administering a therapeutically effective amount of a compound according to any of claims 1-71 to the mammal.

133. A method for increasing blood plasma or serum concentrations of HDL cholesterol of a mammal, which comprises administering a therapeutically effective amount of a compound according to any of claims 1-71 to the mammal.

134. A method for reducing blood plasma or serum concentrations of apolipoprotein B in a mammal, which comprises administering a therapeutically effective amount of a compound according to any of claims 1-71 to the mammal.

135. A method of treating at least one vascular condition while preventing or minimizing muscular degenerative side effects associated with HMG-CoA reductase inhibitors, said method comprising administering to a subject in need thereof a compound according to any of claims 1-71 in combination with at least one HMG-CoA reductase inhibitor.

136. A method of regulating the amount of ApoE isoform 4 in the bloodstream and/or brain of the subject comprising the step of administering to a subject in need of such treatment an effective amount of a composition comprising at least one compound represented by any of claims 1-71.

137. A method of preventing, treating, or ameliorating symptoms of Alzheimer's Disease comprising the step of administering to a subject in need of such treatment an effective amount of a composition comprising at least one compound according to any of claims 1-71.

138. A method of regulating the production of at least one amyloid β peptide in a subject or regulating a level of at least one amyloid β peptide in bloodstream and/or brain of a subject, comprising the step of administering to a subject in need of such treatment an effective amount of a composition comprising at least one compound represented by any of claims 1-71.

139. A method of prevention or treatment of a cholesterol-associated tumor comprising administering a therapeutically effective amount of a compound according

to any of claims 1-71 to a patient at risk of developing a cholesterol-associated tumor or already exhibiting a cholesterol-associated tumor.

140. A method of prevention or treatment of a cholesterol-associated tumor according to claim 139 wherein the cholesterol-associated tumor is selected from the group consisting of benign prostatic hypertrophy, benign breast tumor, benign endometrial tumor, and benign colon tumor.

141. A method of prevention or treatment of a cholesterol-associated tumor according to claim 139 wherein the cholesterol-associated tumor is selected from the group consisting of malignant prostate tumor, breast cancer tumor, endometrial cancer tumor, and colon cancer tumor.

142. A method of prevention or treatment of a cholesterol-associated tumor comprising coadministering a therapeutically effective amount of a compound according to any of claims 1-71 and at least one other anticancer agent to a patient at risk of developing a cholesterol-associated tumor or already exhibiting a cholesterol-associated tumor.

143. A method of prevention or treatment of a cholesterol-associated tumor comprising administering a pharmaceutical formulation according to claim 72 to a patient in need of such prevention or treatment.

144. A method of preventing or decreasing the incidence of xanthomas in a subject comprising administering to a subject in need of such treatment an effective amount of a compound according to any of claims 1-71.

145. A method of preventing or decreasing the incidence of metastases in a subject comprising administering to a subject in need of such treatment an effective amount of a compound according to any of claims 1-71.

FIG. 1

Bioavailability of compounds of the invention

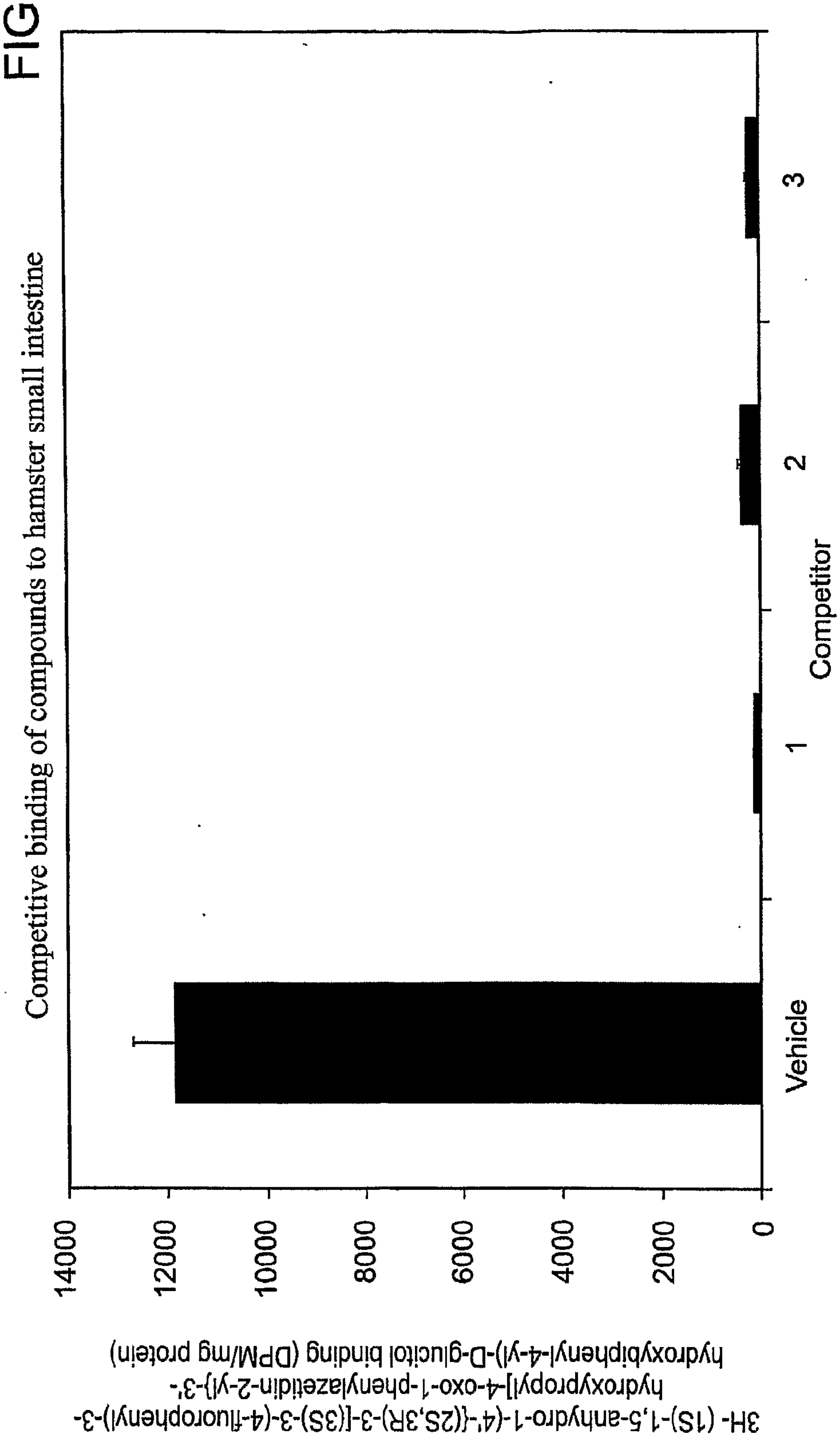
Row	Compound	Animal	fasted/non-fasted	F VALUE (%)
1	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4 oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol	monkey	fasted	0.1
2	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4 oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol	dog	non-fasted	0.12
3	(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid	rat	fasted	0.2
4	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4 oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol	dog	fasted	0.35
5	(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)phosphonic acid	rat	fasted	0.5
6	(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)phosphonic acid	rat	fasted	1.05
7	4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-sulfonic acid	rat	fasted	4
8	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4 oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol	rat	non-fasted	<0.15
9	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4 oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol	rat	fasted	<0.3, <0.2
10	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4 oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol	hamster	fasted	<0.4, <0.05
11	(1x)-1,5-anhydro-1-(4'-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}biphenyl-3-yl)-L-glucitol	rat	fasted	<0.9
12	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4 oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-yl)-D-glucitol	rat	fasted	<3.2
13	4'-{(2S,3R)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-3-sulfonic acid	rat	fasted	<3.7
14	(3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one	rat	fasted	55

ACAT inhibition activity of compounds of the invention

Row	Compound	HepG2 cells IC_{50} (μM)	Caco2 cells IC_{50} (μM)
1	N-[4-(2-chlorophenyl)-6,7-dimethyl-3-quinolyl] N'-(2, 4-difluorophenyl) urea	0.18	not determined
2	(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one	6.3	6.5, 5.1
3	(3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one	0.67	0.47, 0.36
4	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol	52	>50, >50
5	(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid	168	>50, >50

FIG. 2

FIG. 3A



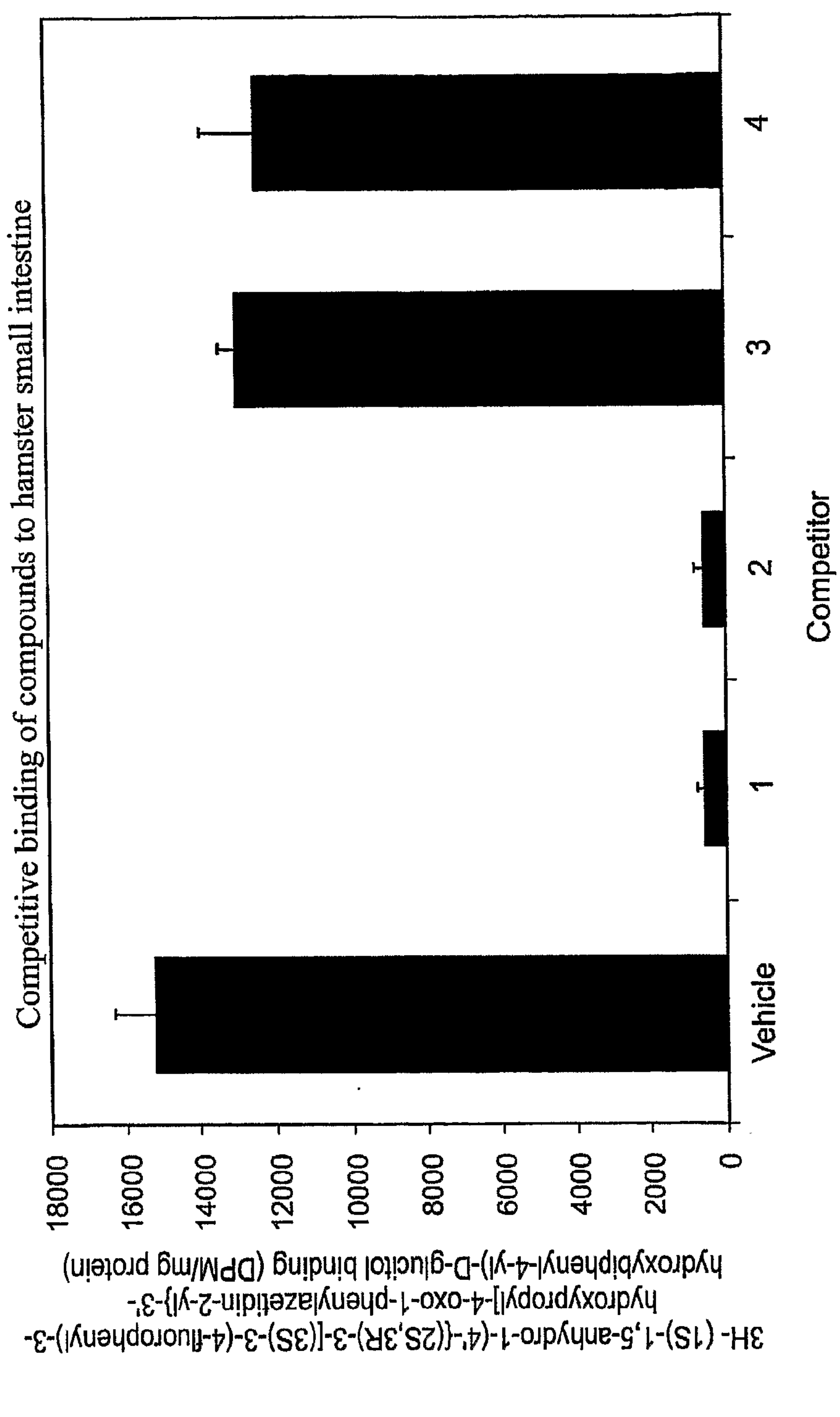
Competitor Compound

1-(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydrozybiphenyl-4-yl)-D-glucicitol

2-(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxypropyl)azetidin-2-one

3-(4'-{(2S,3R)-3-{(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydrozybiphenyl-4-yl)phosphonic acid

FIG. 3B



Competitor Compound
1-(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydrozybiphenyl-4-yl)-D-glucicitol
2-(3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one
3-(3R,4S)-4-(4-fluorobiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3(4-flourophenyl)-3-hydroxypropyl]azetidin-2-one
4-(3R,4S)-4-(2',5-difluorobiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3(4-flourophenyl)-3-hydroxypropyl]azetidin-2-one

Binding of compounds to hamster small intestine

Row	Compound	% ^{3}H-(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol binding*
1	(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol	1.5 +/- 0.4 (4), 3.9 +/- 1.3 (3)
2	(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one	3.5 +/- 0.4 (4)
3	(3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one	3.9 +/- 1.8 (3)
4	(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid	1.8 +/- 0.2 (4)
5	(3R,4S)-4-(4'-fluorobiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one	85.5 +/- 2.9 (3)
6	(3R,4S)-4-(2',5'-difluorobiphenyl-4-yl)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one	82.3 +/- 10.2 (3)

*Calculated as percentage of binding observed in the absence of competitor within an experiment. Values are indicated +/- standard error of the mean with the number of animals/group in parentheses.

FIG. 3C

FIG. 4A

Retinol

Compound (10mg/kg)	^{14}C-cholesterol absorption (mean ± SEM)	^{3}H-retinol absorption (mean ± SEM)
(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one	11 ± 2%	112 ± 7%
(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol	17 ± 3%	141 ± 19%
(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid	16±2%	83±6%
(3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one	12±0%	98±7%

FIG. 4B

Taurocholic acid

Compound (10mg/kg)	^{14}C-cholesterol absorption (mean ± SEM)	^{3}H-taurocholic acid absorption (mean ± SEM)
(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one	14 ± 1%	79 ± 19%
(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol	22 ± 4%	102 ± 9%
(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid	22±4%	53±18%
(3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one	16±1%	101±16%

FIG. 4C

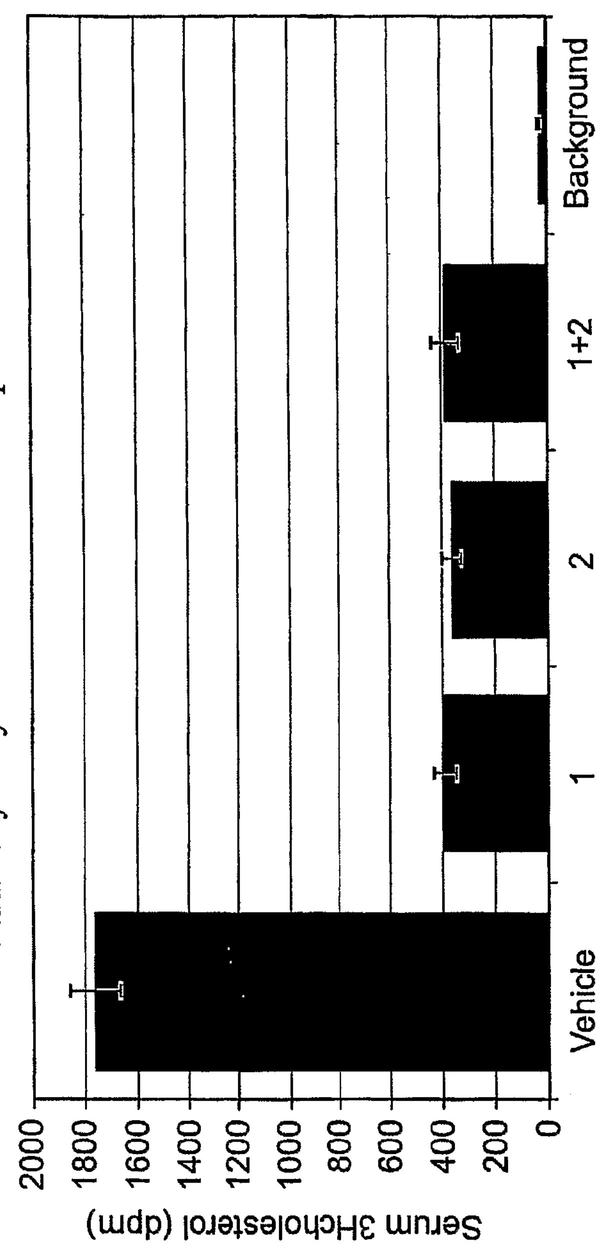
Progesterone

Compound (10mg/kg)	^{14}C-cholesterol absorption (mean ± SEM)	^{3}H-progesterone absorption (mean ± SEM)
(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one	25 ± 5%	102 ± 3%
(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol	19 ± 3%	108 ± 7%
(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid	9±4%	82±10%
(3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one	22±4%	107±11%

FIG. 4D

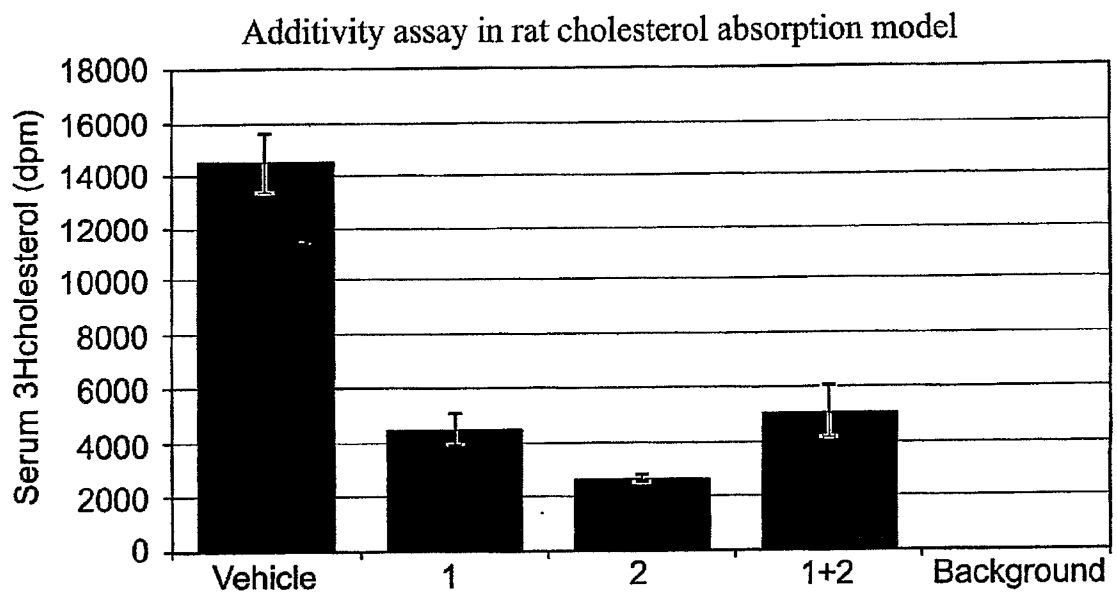
Sitostanol

Compound (10mg/kg)	^{14}C-cholesterol absorption (mean ± SEM)	^{3}H-sitostanol absorption (mean ± SEM)
(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one	81 ± 4%	68 ± 5%
(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol	72 ± 4%	71 ± 4%
(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid	17±4%	61±4%
(3R,4S)-4-(3,3'-dihydroxybiphenyl-4-yl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one	14±1%	52±4%



Compounds used in assay
1-(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one
2-(3R,4S)-4-(3,3'-dihydroxybiphenyl-4-y)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-phenylazetidin-2-one

FIG. 5A

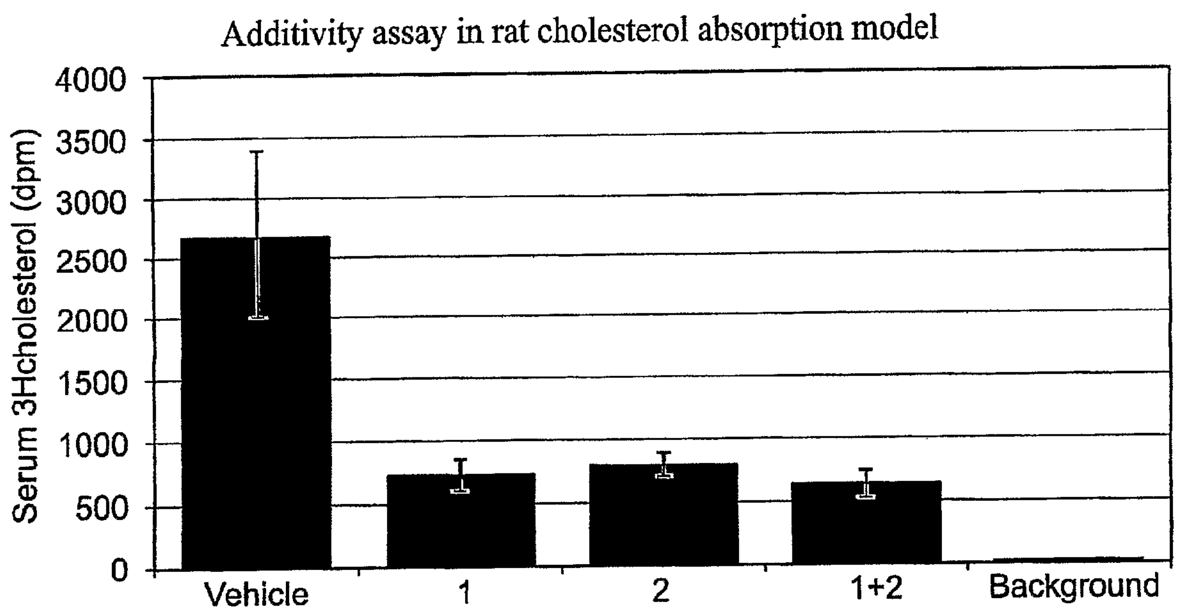


Compounds used in assay

1- (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one

2- (4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)phosphonic acid

FIG. 5B



Compounds used in assay

1-(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one

2-(1S)-1,5-anhydro-1-(4'-{(2S,3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-1-phenylazetidin-2-yl}-3'-hydroxybiphenyl-4-yl)-D-glucitol

FIG. 5C